

## 1. NAME OF THE MEDICINAL PRODUCT

Actilyse<sup>®</sup>, powder and solvent for solution for injection and infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Active ingredient:

The reconstituted solution contains 1 mg alteplase/ 1ml or 2 mg alteplase /1 ml.

1 vial with 467 mg powder contains: 10 mg alteplase or

1 vial with 933 mg powder contains: 20 mg alteplase or

1 vial with 2333 mg powder contains: 50 mg alteplase or

1 vial with 4666 mg powder contains: 100 mg alteplase

Alteplase is produced by recombinant DNA technique using a Chinese hamster ovary cell-line. The specific activity of alteplase in-house reference material is 580.000 IU/mg. This has been confirmed by comparison with the second international WHO standard for t-PA. The specification for the specific activity of alteplase is 522,000 to 696,000 IU/mg.

The pH of the reconstituted solution is 7.3 +/- 0.5.

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### *4.1.1. Thrombolytic treatment in acute myocardial infarction*

- 90 minutes (accelerated) dose regimen (see posology and method of administration): for patients in whom treatment can be started within 6 h after symptom onset
- 3 h dose regimen (see posology and method of administration): for patients in whom treatment can be started between 6 - 12 h after symptom onset provided that the a.m. indication is clear

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

#### *4.1.2. 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 is no evidence for positive effects on mortality and late morbidity related to pulmonary embolism.

#### 4.1.3. For fibrinolytic treatment of acute ischaemic stroke.

Treatment must be started within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

## 4.2 Posology and method of administration

Actilyse should be given as soon as possible after symptom onset. The following dose guidelines apply.

Under aseptic conditions the content of an injection vial of Actilyse (10 or 20 or 50 mg) dry substance is dissolved with water for injections according to the following table to obtain either a final concentration of 1 mg alteplase/ml or 2 mg alteplase/ml:

Actilyse vial	10 mg	20 mg	50 mg	100 mg
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### Volume of Water for Injections to be added to dry powder:

Final concentration:

(a) 1 mg alteplase/ml	(ml)	10	20	50	2 x 50
(b) 2 mg alteplase/ml	(ml)	5	10	25	50

The transfer cannulas provided with the packs of Actilyse 20 mg, Actilyse 50 mg and Actilyse 100 mg are to be used for this. In the case of Actilyse 10 mg a syringe should be used.

The reconstituted solution should then be administered intravenously. It may be diluted further with sterile physiological saline solution (0.9 %) up to a minimal concentration of 0.2 mg/ml.

#### 4.2.1. Myocardial infarction

- a) 90 minutes (accelerated) dose regimen for patients with myocardial infarction, in whom treatment can be started within 6 hours after symptom onset:

	Concentration of alteplase	
	1 mg/ml	2 mg/ml
	ml	ml
15 mg as an intravenous bolus	15	7.5
50 mg as an infusion over 30 minutes	50	25
followed by an infusion of 35 mg over 60 minutes, until the maximal dose of 100 mg	35	17.5

In patients with a body weight below 65 kg the dose should be weight adjusted according to the following table:

	Concentration of alteplase	
	1 mg/ml	2 mg/ml
	ml	ml
15 mg as an intravenous bolus	15	7.5
	ml/kg bw	ml/kg bw
and 0.75 mg/kg body weight (bw) over 30 minutes (maximum 50 mg)	0.75	0.375
followed by an infusion of 0.5 mg/kg body weight (bw) over 60 minutes (maximum 35 mg)	0.5	0.25

- b) 3 h dose regimen for patients, in whom treatment can be started between 6 and 12 hours after symptom onset:

	Concentration of alteplase	
	1 mg/ml	2 mg/ml
	ml	ml
10 mg as an intravenous bolus	10	5
50 mg as an infusion over the first hour	50	25
	ml/30 min.	ml/30 min.
followed by infusions of 10 mg over 30 minutes, until the maximal dose of 100 mg over 3 hours	10	5

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

The maximal accepted dose of alteplase is 100 mg.

**Adjunctive therapy:**

Acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued for the first months after myocardial infarction. The recommended dose is 160 - 300 mg/d.

Heparin should be administered concomitantly at least for 24 hours or longer (at least 48 hours with the accelerated dose regimen). It is recommended to start with an initial intravenous bolus of 5,000 IU prior to thrombolytic therapy and to continue with an infusion of 1,000 IU/hour. The dose of heparin should be adjusted according to repeated measurements of aPTT values of 1.5 to 2.5 fold of the initial value.

#### 4.2.2. Pulmonary embolism

A total dose of 100 mg of alteplase should be administered in 2 hours. The most experience available is with the following dose regimen:

	Concentration of alteplase	
	1 mg/ml	2 mg/ml
	ml	ml
10 mg as an intravenous bolus over 1 – 2 minutes	10	5
followed by an intravenous infusion of 90 mg over 2 hours	90	45

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 aPTT values are less than twice the upper limit of normal. The infusion should be adjusted according to aPTT values of 1.5 to 2.5 fold of the initial value.

#### 4.2.3. Acute ischaemic stroke

Treatment must be performed by a physician specialised in neurological care. (See contraindications and special warnings/ precautions for use.)

The recommended dose is 0.9 mg substance/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus.

Treatment with Actilyse must be started within 3 hours of the onset of symptoms.

#### **Adjunctive therapy:**

The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid within the first 24 hours of onset of the symptoms have not been sufficiently investigated. 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.

### 4.3 Contra-indications

Like all thrombolytic agents, Actilyse should not be used in cases where there is a high risk of haemorrhage such as:

- known haemorrhagic diathesis
- patients receiving oral anticoagulants, e.g. warfarin sodium.
- manifest or recent severe or dangerous bleeding
- known history of or suspected intracranial haemorrhage
- suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- haemorrhagic retinopathy, e. g. in diabetes (vision disturbances may indicate haemorrhagic retinopathy)

- recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- severe uncontrolled arterial hypertension
- bacterial endocarditis, pericarditis
- acute pancreatitis
- documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations
- neoplasm with increased bleeding risk
- severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis.
- major surgery or significant trauma in past 3 month

**4.3.1 Additional contraindications in acute myocardial infarction:**

any history of stroke

**4.3.2 Additional contraindications in acute pulmonary embolism:**

any history of stroke

**4.3.3 Additional contraindications in acute ischaemic stroke:**

- symptoms of ischaemic attack began more than 3 hours prior to infusion start or when time of symptom onset is unknown,
- minor neurological deficit or symptoms rapidly improving before start of infusion,
- severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques,
- seizure at onset of stroke,
- evidence of intracranial haemorrhage (ICH) on the CT-scan,
- symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal,
- administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory,
- patients with any history of prior stroke and concomitant diabetes
- prior stroke within the last 3 months
- platelet count of below 100,000/mm<sup>3</sup>
- systolic blood pressure > 185 or diastolic BP > 110 mm Hg, or aggressive management (IV medication) necessary to reduce BP to these limits
- blood glucose < 50 or > 400 mg/dl (<2.8 or >22.2 mmol/L).

**Use in children and elderly patients**

Actilyse is not indicated for the treatment of acute stroke in children under 18 years or adults over 80 years of age.

**4.4 Special warnings and special precautions for use**

Thrombolytic/ fibrinolytic treatment requires adequate monitoring. Actilyse should only be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use.

The risk of intracranial haemorrhage is increased in elderly patients, therefore in these patients the risk/benefit evaluation should be carried out carefully.

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

As with all thrombolytic agents, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with :

- small recent traumas, such as biopsies, puncture of major vessels, intramuscular injections, cardiac massage for resuscitation
- conditions with an increased risk of haemorrhage which are not mentioned in chapter 4.3.

The use of rigid catheters should be avoided.

#### **4.4.1 Additional special warnings and precautions in acute myocardial infarction:**

A dose exceeding 100 mg of alteplase must not be given because it has been associated with an additional increase in intracranial bleeding.

Therefore special care must be taken to ensure that the dose of alteplase infused is as described in section 4.2 Posology and Method of Administration.

There is limited experience with readministration of Actilyse. Actilyse is not suspected to cause anaphylactic reactions. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment initiated.

As with all thrombolytic agents, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with systolic blood pressure > 160 mm Hg.

#### **4.4.2 Additional special warnings and precautions in acute pulmonary embolism:**

Same as for acute myocardial infarction (4.4.1).

#### **4.4.3 Additional special warnings and special precautions in acute ischaemic stroke :**

##### **Special precautions for use**

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

##### **Special warnings / conditions with a decreased benefit/risk ratio**

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 4.3. and in general all situations involving a high risk of haemorrhage
- small asymptomatic aneurysms of the cerebral vessels
- patients pre-treated with acetylsalicylic acid (ASA, aspirin) 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 treatment should not be initiated later than 3 hours after the onset of symptoms (see 4.3 contra-indications) because of an unfavourable benefit/risk ratio mainly based on the following:

- positive treatment effects decrease over time
- mortality rate increases particularly in patients with prior acetylsalicylic acid (ASA, aspirin) treatment
- risk increases with regard to symptomatic haemorrhages

Blood pressure (BP) monitoring during treatment administration and up to 24 hours seems justified; an i.v. antihypertensive therapy is also recommended if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg.

The therapeutic benefit is reduced in patients that have had a prior stroke or in those with known uncontrolled diabetes, thus the benefit/risk ratio is considered less favourable, but still positive, in these patients.

In patients with very mild stroke, the risks outweigh the expected benefit (see 4.3 contra-indications).

Patients with very severe stroke are at higher risk for intracerebral haemorrhage and death and should not be treated (see 4.3 contra-indications).

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 good outcomes 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 bleedings increases, independently from treatment. Patients over 80, 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 (< 2.8 or > 22.2 mmol/L) at baseline should not be treated with Actilyse (see 4.3 contra-indications).

#### **Other special warnings**

Reperfusion of 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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The risk of haemorrhage is increased if coumarin derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or other agents inhibiting coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse) (see 4.3 contra-indications).

#### **4.6 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.

In pregnant animals no teratogenic effects were observed after iv. infusion of pharmacologically effective doses. In rabbits embryotoxicity (embryo lethality, 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.

#### **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 resulting in a fall in haematocrit and/or haemoglobin values. 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 bleedings into the gastro-intestinal or uro-genital tract, retro-peritoneum or CNS or bleeding of parenchymatous organs.

Symptomatic intracerebral haemorrhage is the main adverse event of Actilyse in treatment of acute ischaemic stroke (up to 10% of patients).

In clinical studies with Actilyse significant blood-loss was observed occasionally from gastro-intestinal, uro-genital or retro-peritoneal bleeding. Ecchymosis, epistaxis and gingival bleeding are observed rather frequently but usually do not require any specific action. In studies, where patients were treated according to clinical routine, i.e. without acute left-heart catheterisation, a blood transfusion was only occasionally necessary. In the treatment of acute myocardial infarction and acute pulmonary embolism intracranial haemorrhage was rarely reported (less than 1 %).

If a potentially dangerous haemorrhage occurs in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued. In general, however, it is not necessary to replace the coagulation factors because of the short half-life and the minimal effect on the systemic coagulation factors. Most patients who have bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement, and manual pressure applied to an incompetent vessel. Protamine should be considered if heparin has been administered within 4 hours of 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 are available as a last alternative.

Actilyse therapy may lead to cholesterol crystal embolisation or thrombotic embolisation in rare cases. In the organs concerned, this may lead to corresponding consequences (e.g. renal failure in the case of renal involvement).

In patients receiving Actilyse for myocardial infarction successful reperfusion is often accompanied by arrhythmias. These may require the use of conventional antiarrhythmic therapies.

Patients with myocardial infarction or pulmonary embolism may experience disease-related events such as cardiac failure, recurrent ischaemia, angina, cardiac arrest, cardiogenic shock, reinfarction, valve disorders (e.g. aortic valve rupture), and pulmonary embolism. These events have also been reported following thrombolytic therapy and can be life-threatening and may lead to death.

In rare cases nausea, vomiting, drop in blood pressure and increased temperature have been reported. These reactions can also occur as concomitant symptoms of myocardial infarction.

As with other thrombolytic agents, events related to the central nervous system (e.g. convulsions) have been reported in isolated cases, often in association with concurrent ischaemic or haemorrhagic cerebrovascular events.

In rare cases, anaphylactoid reactions have been reported. These 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 allergic reactions. If they occur, conventional anti-allergic therapy should be initiated. 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.

#### **4.9 Overdose**

The relative fibrin specificity notwithstanding, a clinical 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.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmaco-therapeutic group: antithrombotic agent, ATC-code: B 01 A D 02

The active ingredient of Actilyse is alteplase, 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.

##### **Studies in myocardial infarction**

In a study including more than 40,000 patients with an acute myocardial infarction (GUSTO) the administration of 100 mg alteplase over 90 minutes, with concomitant iv. heparin infusion, led to a lower mortality after 30 days (6.3 %) as compared to the administration of streptokinase, 1.5 million U over 60 minutes, with s.c. or iv. heparin (7.3 %). 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.

30-day-mortality is reduced as compared to patients not undergoing thrombolytic therapy.

The release of alpha-hydroxybutyrate-dehydrogenase (HBDH) is reduced. Global ventricular function as well as regional wall motion is less impaired as compared to patients receiving no thrombolytic therapy.

A placebo controlled trial with 100 mg alteplase over 3 hours (LATE) showed a reduction of 30-day-mortality compared to placebo for patients treated within 6-12 hours after symptom onset. In cases, in which clear signs of myocardial infarction are present, treatment initiated up to 24 hours after symptom onset may still be beneficial.

##### **Studies in pulmonary embolism**

In patients with acute massive pulmonary embolism with haemodynamic instability thrombolytic treatment with Actilyse leads to a fast reduction of the thrombus size and a reduction of pulmonary artery pressure. Mortality data are not available.

##### **Studies in acute stroke**

In two USA studies (NINDS A/B) a significant higher proportion of patients, when compared to placebo, had a favourable outcome (no or minimal disability). These findings were not confirmed in two European studies and an additional USA study. In the latter studies however, the majority of patients were not treated within 3 hours of stroke onset. In a meta-analysis of all patients treated within 3 hours after stroke onset the beneficial effect of alteplase was confirmed. The risk difference versus placebo for a good recovery was 14.9% (CI 95% 8.1% to 21.7%) despite an increased risk of severe and fatal intracranial haemorrhage. The data do not

allow drawing a definite conclusion on the treatment effect on death. Nevertheless overall, the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the precautions stated elsewhere in the SPC, is considered favourable.

Meta-analysis of all clinical data show that the agent is less effective in patients treated after 3 hours of onset (3 to 6 hours) compared with those treated within 3 hours of onset of symptoms, while the risks are higher, which makes the benefit/risk ratio of alteplase unfavourable outside the 0-3h time frame.

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.

## **5.2 Pharmacokinetic properties**

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 ml/min.). The relevant plasma half-life  $T_{1/2}$  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 unexpected side effects were found. No indications of a mutagenic potential were found in mutagenic tests.

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

### **Powder for solution:**

L-arginine  
Phosphoric acid, 10%,  
Polysorbate 80

### **Solvent:**

Water for injections

## **6.2 Incompatibilities**

The reconstituted solution may be diluted further with sterile physiological saline solution (0.9 %) up to 1:5.

It may not, however, be diluted further with water for injections or carbohydrate infusion solutions, e. g. dextrose.

Actilyse must not be mixed with other drugs, neither in the same infusion-vial nor via the same catheter (not even with heparin).

## **6.3 Shelf life**

36 months

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 2 - 8°C and 8 hours at 25°C. From a microbiological point of view, the product should be used immediately.

#### **6.4 Special precautions for storage**

Do not store above 25°C.  
Protect from light. Store in the original package.

#### **6.5 Nature and contents of container**

##### **Powder for solution:**

10, 20, 50 or 100 ml sterilised glass vials, which are stoppered with sterile siliconised grey butyl-lyophilisation-type stoppers with aluminium/plastic flip-off caps.

##### **Solvent:**

The water for injections is filled into either 10, 20, 50 or 2 x 50 ml vials, depending on the size of the rt-PA vials. The water for injections vials are stoppered with appropriate rubber stoppers and aluminium/plastic flip-off type caps.

**Transfer cannulas (included with pack-sizes of 20 mg, 50 mg and 100 mg only)**

##### **Pack sizes:**

###### ***10 mg***

1 vial with 467 mg powder for solution for infusion  
1 vial with 10 ml of water for injections

###### ***20 mg***

1 vial with 933 mg powder for solution for infusion  
1 vial with 20 ml of water for injections  
1 transfer cannula

###### ***50 mg***

1 vial with 2333 mg powder for solution for infusion  
1 vial with 50 ml of water for injections  
1 transfer cannula

###### ***100 mg***

1 vial with 4666 mg powder for solution for infusion  
2 vials with 50 ml of water for injections  
2 transfer cannulas

#### **6.6 Instructions for use and handling**

None

### **7. MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim Limited  
Ellesfield Avenue  
Bracknell

Berkshire  
RG12 8YS  
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**8. MARKETING AUTHORISATION NUMBER(S)**

PL 00015/0120

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

12 October 1988 / 26 April 1999

**10. DATE OF REVISION OF THE TEXT**

October 2002