Actilyse®
Alteplase

Powder and solvent for solution for injection

Composition

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

excipients: l-arginine, phosphoric acid, polysorbate 80
Trace residue : gentamicin from manufacturing process

The reconstituted solution contains 1 mg alteplase per mL.

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

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.

Dosage and administration
Dosage
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 an intravenous infusion of
- 40 mg 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, 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.

Acute massive pulmonary embolism

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).

Acute ischaemic stroke

The recommended total dose is 0.9 mg alteplase/kg bodyweight (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 WARNING 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.

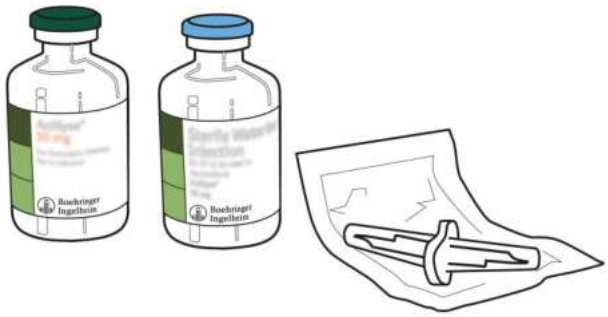
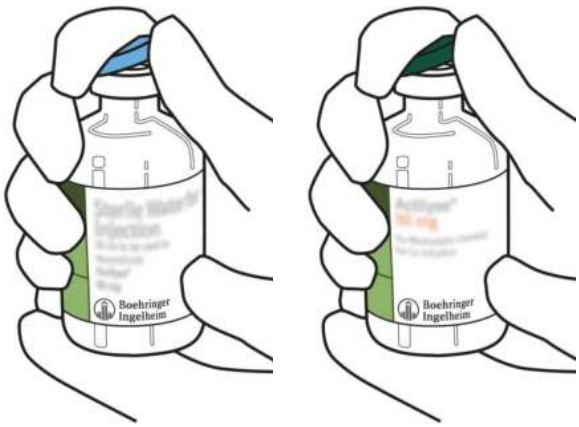
Handling Instructions

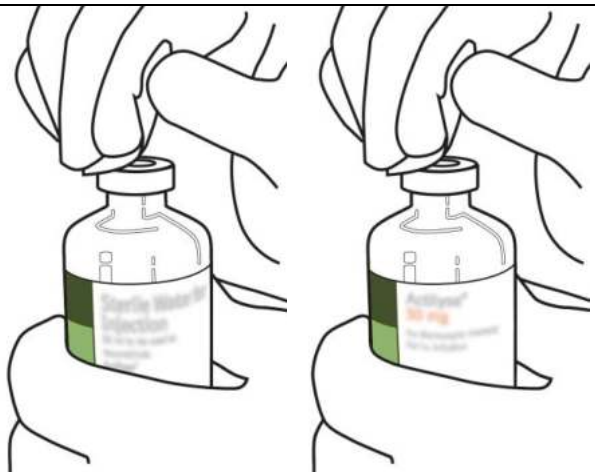
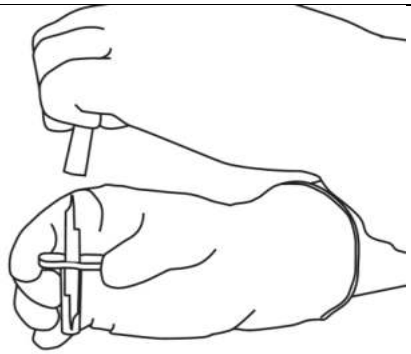
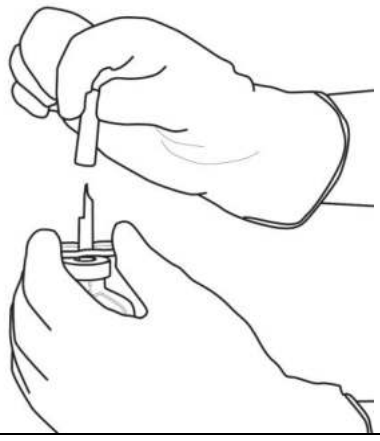
Under aseptic conditions the contents of an injection vial of ACTILYSE 50 mg dry substance is dissolved with sterilised water for injection according to the following table to obtain a final concentration of 1 mg alteplase per mL.

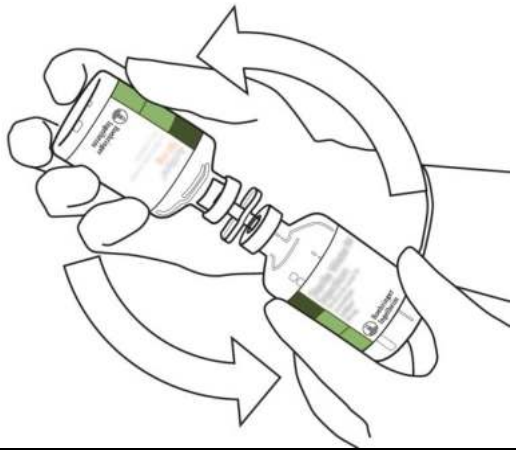
ACTILYSE dry substance	50 mg
Volume of sterilised water for injections to be added to dry substance	50 mL
Final concentration:	1 mg alteplase/mL

For this purpose a transfer cannula is included with the pack-sizes of 50 mg. For the pack-size 10 mg a syringe should be used.

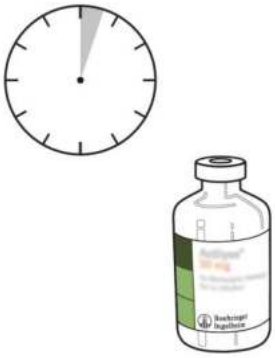
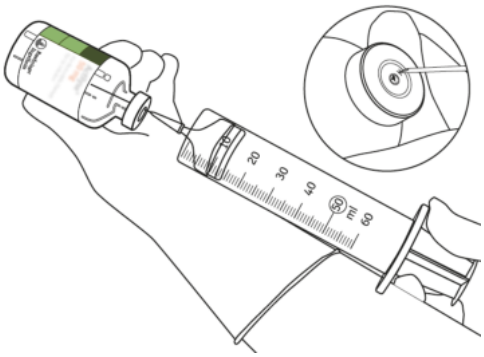
Instructions for reconstituting Actilyse

1	Reconstitute immediately before administration.	
2	Remove the protective cap on the two vials containing the sterile water and Actilyse dry substance by flipping them up with a thumb.	

3	Swab the rubber top of each vial with an alcohol wipe.	
4	Remove the transfer cannula* from its cover. Do not disinfect or sterilize the transfer cannula; it is sterile. Take one cap off.	
5	Stand the sterile water vial upright on a stable surface. From directly above, puncture the rubber stopper vertically in the stopper centre with the transfer cannula, by pressing gently but firmly, without twisting.	 Sterile water for injection
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 centre of the stopper. Push down the vial with the dry substance onto the transfer cannula from directly above, puncturing the rubber stopper vertically and gently but firmly without twisting.	  Actilyse (dry substance) ⇩ Sterile water for injection
8	Invert the two vials and allow the water to drain completely into the dry sustance.	

		Sterile water for injection  Sterile water for injection ⇩ Actilyse (dry substance)
9	Remove the empty water vial together with the transfer cannula. They can be disposed of.	

10	Take the vial with reconstituted Actilyse and swirl gently to dissolve any remaining powder, but do not shake, as this will produce foam. If there are bubbles, let the solution stand undisturbed for a few minutes to allow them to disappear.	 
11	The **reconstituted** solution consists of 1mg/mL Actilyse. It should be clear and colourless to pale yellow and it should not contain any particles.	
12	Remove the amount required only by using a needle and a syringe. Do not use the puncture location from the transfer cannula to avoid leakage.	
13	Use immediately. Dispose of any unused solution.	

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

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).

Special precautions for storage

Shelf life: 36 Months.
Store below 30°C
Keep out of reach of children. Protect from light

Chemical and physical in-use stability
The reconstituted solution has been demonstrated to be stable for 24 hours at 2-8°C and for 8 hours at 30°C

Microbiological in-use stability
From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8°C.

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 anticoagulants treatment, (e.g. warfarin sodium with INR > 1.3) (please see section SPECIAL WARNING 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 indication acute myocardial infarction and 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 (< 2.8 mmol/L or > 22.2 mmol/L)

ACTILYSE is not indicated for the therapy of acute stroke in children and adolescents under 18 years.

Special 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 infraction, acute massive pulmonary embolism or acute ischaemic stroke (due to risk of massive under dosing). Only the 10 mg, 20 mg and 50 mg presentations are indicated for use in these indications.

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

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

Immune-mediated hypersensitivity reactions associated with the administration of ACTILYSE can be caused by the active substance alteplase or any of the excipients (see also section CONTRAINDICATIONS).

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

Angio-oedema represents the most common hypersensitivity reaction reported with ACTILYSE®. This risk may be enhanced in the indication acute ischaemic stroke and/or by concomitant treatment with ACE inhibitors (see section 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 anticoagulants 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.
Referfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of the conventional antiarrhytmic therapies.

Glyco-ProteinIIb/IIIa receptor antagonists

The concomitant use of GPIIb/IIIa receptor 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 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 a physician trained and experienced in neurological care. For the verification of treatment indication remote diagnostic measures may be considered as appropriate (see section Indications; 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. 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. Therefore, the use of ACTILYSE® should be weighed carefully against.

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.

Interactions
No formal interaction studies with ACTILYSE and medicinal products commonly administered in patients with acute myocardial infarction have been performed.

Drugs 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 CONTRAINDICATIONS.

ACE inhibitors
Concomitant treatment with ACE inhibitors may enhance the risk of suffering a hypersensitivity reaction (see section SPECIAL WARNING AND PRECAUTIONS).

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 TOXICOLOGY).

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. Nonclinical studies performed with alteplase showed no adverse effect on fertility (TOXICOLOGY).

Effects on ability to drive and use machines
Not applicable.

Side 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
- angiooedema
- 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 arrhythmias, 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.

Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

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

Overdose
Symptoms
If the maximum recommended dose is exceeded the risk of intracranial bleeding increases. The relative fibrin specificity notwithstanding, a clinical 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.

Pharmacological 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 ~~s.c.~~ 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. Therefore, treatment decisions in this patient group require particular care on an individual patient basis.
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 $\geq$ 95), Modified Rankin Scale (score $\leq$ 1), Glasgow Outcome Scale (score = 1), and NIHSS (score $\leq$ 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) [104] 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 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 from onset of symptoms 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%.

Elderly patients

Individual patient data adjusted meta-analyses from 6,756 patients including those aged > 80 years in nine randomised trials comparing alteplase with placebo or open control were used to assess the benefit-risk of alteplase in patients > 80 years.

The effect of alteplase treatment was similar for patients aged 80 years or younger [mean treatment delay 4.1 hours: 990/2512 (39%) alteplase treated vs 853/2515 (34%) controls achieved good stroke outcome at day 90/180; OR 1.25, 95% CI 1.10-1.42] and for those older than 80 years [mean treatment delay 3.7 hours: 155/879 (18%) alteplase treated vs 112/850 (13%) controls achieved good stroke outcome; OR 1.56, 95% CI 1.17-2.08].

In patients older than 80 years treated with alteplase less or equal to 3 hours, a good stroke outcome was achieved in 55/302 (18.2%) vs 30/264 (11.4%) in controls (OR 1.86, 95% CI 1.1-3.13) and those treated with alteplase 3 hours-4.5 hours 58/342 (17.0%) achieved a good stroke outcome vs 50/364 (13.7%) in controls (OR 1.36, 95% CI 0.87-2.14).

Based on the same database, an additional meta-analysis, which included a cohort of patients who met the European registered label (SmPC) selection criteria but without age restriction, was performed. The results showed that the probability of a good stroke outcome (mRS 0-1 at day 90/180) was increased up to 4.5 hours from stroke onset with a larger benefit when treated earlier (p-value for interaction of 0.0203) and was independent of age (p-value = 0.7383).

Type 2 parenchymal haemorrhage within 7 days occurred in 231/3,391 (6.8%) assigned to alteplase versus 44/3,365 (1.3%) assigned to control (OR 5.55, 95% CI 4.01-7.70). Fatal type 2 parenchymal haemorrhage within 7 days occurred in 91 (2.7%) patients assigned to alteplase versus 13 (0.4%) assigned to control (OR 7.14, 95% CI 3.98-12.79).

In patients older than 80 years treated by alteplase a fatal intracranial haemorrhage within 7 days occurred in 32/879 (3.6%) vs 4/850 (0.5%) in controls (OR 7.95, 95% CI 2.79-22.60).

Acute ischemic stroke patients > 80 years are at higher risk for a poor outcome due to their age and due to higher baseline NIHSS score. The alteplase treatment in acute ischemic stroke patients >80 years increases the incidence of good stroke outcome (mRS score 0-1) at 90/180 days without an increase in 90-day mortality in comparison to non-treated over 80 years old acute ischemic stroke patients. The risk of sICH in alteplase treated acute ischemic stroke patients over 80 years is similarly increased as in younger patients.

From a total of 8,658 patients > 80 years treated < 4.5 hours of stroke onset in the SITS-ISTR, the data of the 2,157 patients treated > 3 to 4.5 hours from stroke onset were compared to those of the 6,501 patients treated < 3 hours.

Three-month functional independence (mRS score 0 - 2) was 36 vs 37% (adjusted OR 0.79, 95% CI 0.68- 0.92), mortality was 29.0% vs 29.6% (adjusted OR 1.10, 95% CI 0.95-1.28), and sICH (per SITS-MOST definition) was 2.7% vs 1.6% (adjusted OR 1.62, 95% CI 1.12-2.34).

Pharmacokinetics

ACTILYSE 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.

Toxicology

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.

Availability

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

Box, 1 vial @ 50 mg + 1 vial pelarut @ 50 ml + 1cannula transfer
Reg. No. DKI9052500344A1

Box, 2 box @ 1 vial @ 50 mg + 1 vial pelarut @ 50 ml + 1 cannula transfer
Reg. No. DKI9052500344A1

Store in a safe place out of the reach of children!
Only on doctor's prescription
Harus dengan resep dokter

Manufactured by :
Boehringer Ingelheim Pharma GmbH & Co.KG
Biberach/Riss, Germany

For:
Boehringer Ingelheim International GmbH, Germany
Ingelheim am Rhein, Germany

Imported by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

Brosur kemasan: Informasi untuk pengguna
Serbuk Actilyse 50 mg dan pelarut untuk larutan injeksi
Alteplase

Baca semua isi brosur ini dengan seksama sebelum Anda mulai menggunakan obat ini karena berisi informasi penting untuk Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya lagi suatu saat.
- Jika Anda mempunyai pertanyaan lebih lanjut, tanyakan kepada dokter atau perawat Anda.
- Jika Anda mendapat efek samping, bicarakan dengan dokter atau perawat Anda. Termasuk juga efek samping yang mungkin tidak tercantum dalam brosur ini. Lihat bagian 4 dari brosur ini.

Apa saja yang ada di dalam selebaran ini:

1. Apakah itu Actilyse dan digunakan untuk apa

Zat aktif di Actilyse adalah alteplase. Itu termasuk kelompok obat yang disebut obat trombolitik.Obat-obatan semacam ini bekerja dengan melarutkan gumpalan darah yang terbentuk di pembuluh darah.
Actilyse 50 mg digunakan untuk mengobati sejumlah gangguan yang disebabkan oleh pembekuan darah yang terbentuk di dalam pembuluh darah, termasuk:
- Pengobatan trombolitik pada infark miokard akut
- Pengobatan trombolitik pada emboli paru masif akut dengan ketidakstabilan hemodinamik
- Pengobatan trombolitik pada stroke iskemik akut

2. Apakah yang perlu Anda ketahui sebelum Anda menggunakan Actilyse

Anda tidak boleh menggunakan Actilyse:
- jika Anda alergi (hipersensitif) terhadap zat aktif alteplase.
- jika Anda mempunyai, atau belum lama ini menderita, penyakit yang meningkatkan risiko perdarahan, termasuk di antaranya:
  - gangguan perdarahan atau kecenderungan mudah berdarah
  - perdarahan yang parah atau berbahaya di bagian tubuh mana pun
  - perdarahan di dalam otak atau tengkorak
  - tekanan darah sangat tinggi yang tidak terkontrol
  - infeksi bakteri atau radang jantung (endokarditis), atau radang selaput di sekitar jantung (perikarditis)
  - radang pankreas (pankreatitis akut)
  - tukak lambung atau tukak di usus
  - varises di kerongkongan (varises esofagus)
  - kelainan pembuluh darah, seperti pembengkakan arteri yang terlokalisir (aneurisma)
  - tumor-tumor tertentu
  - penyakit hati yang parah
- jika Anda minum obat yang digunakan untuk "mengencerkan" darah (antikoagulan oral), kecuali jika sudah dites secara tepat dan ditegaskan tidak ada aktivitas yang secara klinis relevan dari obat tersebut
- jika Anda pernah menjalani operasi pada otak atau tulang belakang Anda

- jika belum lama ini Anda menjalani operasi besar atau cedera signifikan dalam 10 hari terakhir
- jika Anda mengalami tusukan pembuluh darah besar belum lama ini
- jika Anda telah diberi pijatan jantung eksternal dalam 10 hari terakhir
- jika Anda melahirkan bayi dalam 10 hari terakhir

Dokter Anda juga tidak akan memberikan Actilyse untuk pengobatan serangan jantung atau pembekuan darah di arteri paru-paru

- jika Anda pernah atau sedang mengalami stroke yang disebabkan oleh perdarahan di otak (stroke hemoragik)
- jika Anda pernah atau sedang mengalami stroke yang penyebabnya tidak diketahui
- jika Anda belum lama ini (dalam 6 bulan terakhir) mengalami stroke yang disebabkan oleh gumpalan darah di arteri otak (stroke iskemik), kecuali ini adalah stroke yang akan diobati

Selain itu dokter Anda tidak akan memberikan Actilyse untuk pengobatan stroke yang disebabkan oleh bekuan darah di arteri otak (stroke iskemik akut)

- jika gejala stroke Anda mulai lebih dari 4,5 jam yang lalu atau jika ada dugaan bahwa gejalanya dimulai lebih dari 4,5 jam yang lalu, karena Anda tidak tahu kapan gejalanya mulai terjadi
- jika stroke Anda hanya menyebabkan gejala yang sangat ringan
- jika ada tanda-tanda perdarahan di otak
- jika Anda mengalami stroke dalam tiga bulan terakhir
- jika gejalanya membaik dengan cepat sebelum menerima Actilyse
- jika Anda mengalami stroke yang sangat parah
- jika Anda mengalami kejang-kejang (konvulsi) ketika stroke Anda mulai
- jika waktu tromboplastin Anda (tes darah untuk melihat seberapa baik pembekuan darah Anda) tidak normal. Tes ini bisa abnormal jika Anda telah menerima heparin (obat yang digunakan untuk "mengencerkan" darah) dalam waktu 48 jam sebelumnya.
- jika Anda menderita diabetes dan pernah mengalami stroke sebelumnya
- jika jumlah keping darah (trombosit) dalam darah Anda sangat rendah
- jika Anda memiliki tekanan darah sangat tinggi (di atas 185/110) yang hanya dapat dikurangi dengan suntikan obat-obatan
- jika jumlah gula (glukosa) dalam darah Anda sangat rendah (di bawah 50 mg/dl)
- jika jumlah gula (glukosa) dalam darah Anda sangat tinggi (lebih dari 400 mg/dl)
- jika Anda berusia di bawah 18 tahun. (Untuk remaja berusia 18 tahun atau lebih, lihat bagian “Dokter Anda akan melakukan perawatan khusus dengan Actilyse”.)

Dokter Anda akan melakukan perawatan khusus dengan Actilyse

- jika Anda mempunyai reaksi alergi di luar reaksi alergi yang mengancam jiwa (hipersensitivitas parah) terhadap zat aktif alteplase.
- jika Anda mendapat atau baru-baru ini mendapat gangguan lain yang meningkatkan risiko perdarahan, seperti::
  - cedera ringan
  - biopsi (prosedur untuk mendapatkan spesimen jaringan)
  - tusukan pada pembuluh darah besar
  - injeksi intramuskuler
  - pijat jantung eksternal
- jika Anda pernah menerima Actilyse sebelumnya.
- jika Anda berusia di atas 80 tahun, Anda mungkin akan mendapat efek yang lebih buruk terlepas dari pengobatan dengan Actilyse.
- Namun, secara umum risiko-manfaat Actilyse pada pasien di atas 80 tahun adalah positif dan usia saja bukanlah penghalang untuk pengobatan dengan Actilyse

3. Bagaimana cara penggunaan Actilyse

Actilyse akan disiapkan dan diberikan kepada Anda oleh dokter Anda atau oleh seorang profesional perawatan kesehatan. Obat ini bukan untuk diberikan oleh Anda sendiri. Pengobatan dengan Actilyse harus dimulai sesegera mungkin setelah gejala Anda mulai terlihat/ dirasakan.

Ada tiga macam gangguan yang dapat diberikan obat ini:

Serangan jantung (infark miokard akut)

Dosis yang diberikan Anda tergantung pada berat badan Anda. Dosis maksimum Actilyse adalah 100 mg tetapi bisa lebih rendah jika berat Anda kurang dari 65 kg.

Obat ini dapat diberikan dengan dua cara berbeda:

a) Bentuk pemberian selama 90 menit, untuk pasien yang dirawat dalam waktu 6 jam setelah gejalanya mulai. Ini terdiri dari:
   - injeksi awal sebagian dosis Actilyse ke dalam vena
   - infuskan sisa dosis selama 90 menit berikutnya.

b) Bentuk pemberian 3 jam, untuk pasien yang dirawat 6 sampai 12 jam setelah dimulainya gejala. Ini terdiri dari:
   - injeksi awal sebagian dosis Actilyse ke dalam vena
   - infuskan sisa dosis selama 3 jam berikutnya.

Selain Actilyse dokter Anda akan memberi Anda obat lain untuk menghentikan pembekuan darah. Ini akan diberikan sesegera mungkin setelah nyeri dada Anda dimulai.

Gumpalan darah di arteri paru-paru (emboli paru masif akut)

Dosis yang diberikan kepada Anda tergantung pada berat badan Anda. Dosis maksimum Actilyse adalah 100 mg tetapi bisa lebih rendah jika berat Anda kurang dari 65 kg.

Obat ini biasanya diberikan sebagai:

- injeksi awal sebagian dosis Actilyse ke dalam vena
- infuskan sisa dosis selama 2 jam berikutnya.

Setelah perawatan dengan Actilyse, dokter Anda akan memulai (atau melanjutkan) terapi dengan heparin (obat untuk "mengencerkan" darah).

Stroke yang disebabkan oleh bekuan darah di arteri otak (stroke iskemik akut)

Actilyse harus diberikan dalam waktu 4,5 jam sejak gejala pertama. Semakin awal Anda menerima Actilyse, semakin banyak manfaat yang dapat Anda peroleh dari pengobatan ini dan semakin kecil kemungkinannya efek samping yang berbahaya terjadi. Dosis yang diberikan kepada Anda tergantung pada berat badan Anda. Dosis maksimum obat ini adalah 90 mg tetapi bisa lebih rendah jika berat Anda kurang dari 100 kg. Actilyse diberikan sebagai:

- injeksi awal sebagian dosis ke dalam vena
- infus dari sisa dosis selama 60 menit berikutnya.

Anda sebaiknya tidak meminum asam asetilsalisilat selama 24 jam pertama setelah perawatan dengan Actilyse untuk stroke.

Dokter Anda mungkin akan memberi Anda suntikan dengan heparin jika ini diperlukan.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan Actilyse, tanyakan kepada dokter atau profesional kesehatan Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang akan mendapatkannya.

Efek samping yang dijelaskan di bawah ini telah dialami oleh orang yang diberikan Actilyse:

Gangguan sistem imun:

Reaksi anakfilaksis, biasanya ringan, namun pada kasus tertentu dapat menjadi berat.

Gangguan sistem saraf:
Perdarahan intracarnial

Gangguan mata:
Perdarahan di mata

Gangguan jantung:
Perdarahan perikardial

Gangguan pembuluh darah:
- Perdarahan
- Penyumbatan arteri secara tiba-tiba di paru-paru (emboli paru), otak (emboli otak) dan semua area tubuh lainnya (emboli sistemik)
- pendarahan organ parenkim, contohnya perdarahan di hati

Gangguan saluran pernapasan, rongga paru dan dada:
Perdarahan terkait paru, seperti dahak bernoda darah (hemoptisis) atau perdarahan pada saluran pernapasan

Gangguan saluran pencernaan:
- Perdarahan di lambung atau usus, termasuk muntah darah (hematemesis) atau darah di tinja (melanea melena atau perdarahan dubur), perdarahan pada gusi
- perdarahan retroperitoneal
- Mual dan muntah

Gangguan kulit dan jaringan di bawah kulit:
Perdarahan di dalam jaringan tubuh yang menyebabkan memar keunguan (ecchymosis)

Gangguan ginjal dan saluran kemih:
Perdarahan dari saluran kemih atau organ reproduksi, yang dapat menyebabkan darah dalam urin Anda (hematuria)

Gangguan umum dan kondisi lokasi pemberian obat:
Perdarahan atau memar (hematoma) di tempat di mana injeksi diberikan

Investigasi:
- Penurunan tekanan darah
- Peningkatan suhu tubuh

Komplikasi dalam cedera dan keracunan:
- Emboli lemak pada pembuluh darah, yang dapat menyebabkan komplikasi pada organ yang bersangkutan

Prosedur bedah dan medis:
- Transfusi

* Emboli lemak tidak di observasi pada populasi uji klinik, namun terdapat dalam pelaporan spontan.

Untuk efek samping yang myngkin terjadi pada indikasi infark miokard akut:
Ganggunan pada jantung:
- Aritmia reperfusi

Pelaporan efek samping
Jika Anda mendapat efek samping, bicarakan dengan dokter atau perawat Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini.
Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara penyimpanan Actilyse
Biasanya Anda tidak akan diminta untuk menyimpan Actilyse karena obat ini akan diberikan kepada Anda oleh dokter Anda.
Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
Simpan di bawah suhu 30ºC. Simpan dalam kemasan aslinya untuk melindungi dari cahaya.
Actilyse tidak boleh digunakan setelah tanggal kedaluwarsa yang tercantum pada label vial dan karton. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.
Stabilitas setelah direkonstitusi:
Larutan setelah direkonstitusi stabil selama 24 jam pada 2-8°C dan selama 8 jam pada 30°C.

6. Isi pack Actilyse dan informasi lainnya
Actilyse berisi apa
- Zat aktif dari Actilyse adalah alteplase. Setiap vial mengandung 50 mg alteplase. Bahan lainnya adalah arginin, asam fosfat (untuk penyesuaian pH) dan polisorbat 80.
- Pelarutnya adalah air untuk injeksi.

Box, 1 vial @ 50 mg + 1 vial pelarut @ 50 ml + 1cannula transfer
Reg. No. DKI9052500344A1

Box, 2 box @ 1 vial @ 50 mg + 1 vial pelarut @ 50 ml + 1 cannula transfer
Reg. No. DKI9052500344A1

Simpan di bawah suhu 30°C
Simpan di tempat yang aman dan jauhkan dari jangkauan anak-anak.
Harus dengan resep dokter

Diproduksi oleh:
Boehringer Ingelheim Pharma GmbH & Co.KG
Biberach/Riss, Germany

Untuk:
Boehringer Ingelheim International GmbH, Germany
Ingelheim am Rhein, Germany

Diimpor oleh:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

Informasi berikut ini ditujukan hanya untuk profesional perawatan kesehatan:

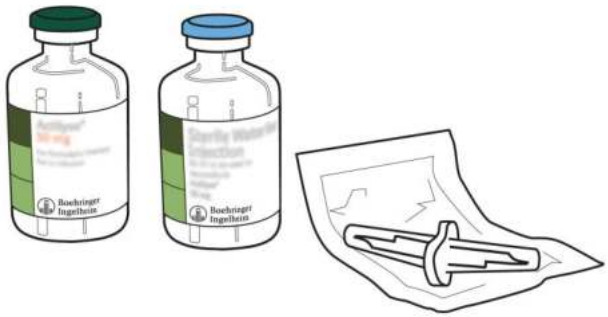
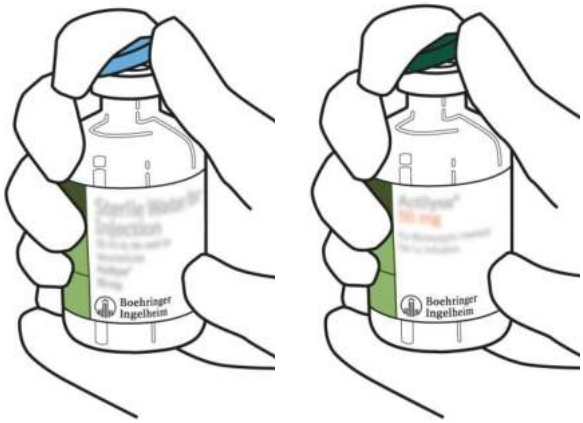
Ketertelusuran
Untuk meningkatkan ketertelusuran produk obat biologi, nama dagang dan nomor bets dari produk yang diberikan harus dicatat dengan jelas dalam file pasien.

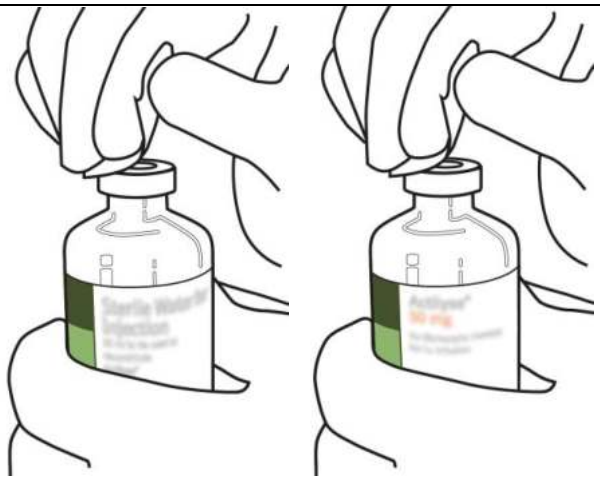
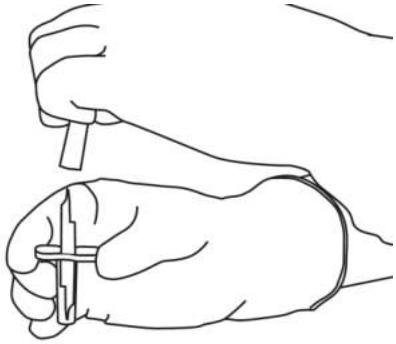
Rekonstitusi

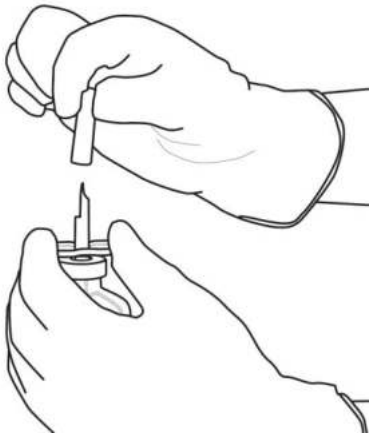
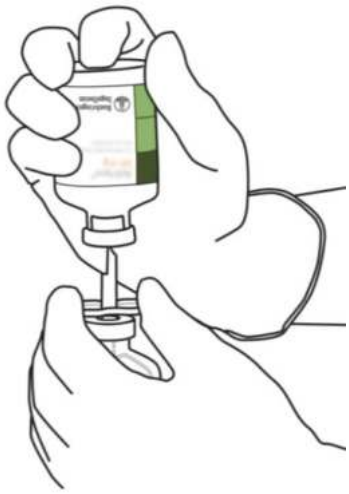
Untuk rekonstitusi sampai konsentrasi akhir 1 mg alteplase per ml, volume penuh pelarut yang disediakan harus dipindahkan ke vial yang mengandung serbuk Actilyse. Untuk tujuan ini kanula transfer dimasukkan dengan sediaan 50 mg ini, yang akan digunakan. Dalam kondisi aseptik, isi vial injeksi Actilyse (50 mg) dilarutkan dengan air untuk injeksi sesuai tabel berikut untuk mendapatkan konsentrasi akhir 1 mg alteplase/ml.

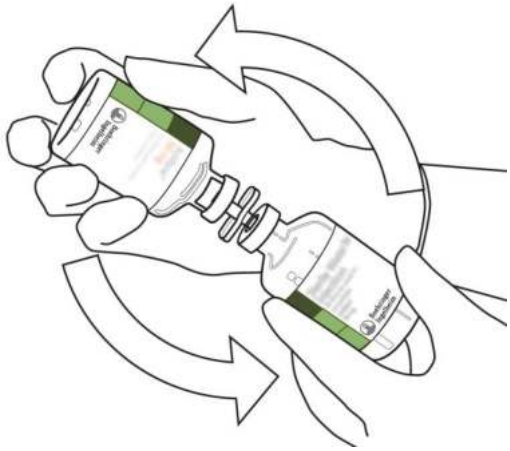
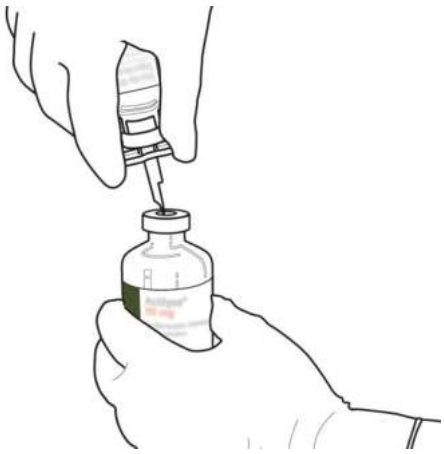
Larutan rekonstitusi kemudian harus diberikan secara intravena. Larutan rekonstitusi 1 mg/mL dapat diencerkan lebih lanjut dengan larutan natrium klorida steril 9 mg/ml (0,9%) untuk injeksi hingga konsentrasi minimal 0,2 mg/ml karena terjadinya kekeruhan dari larutan rekonstitusi tidak dapat dikecualikan. Pengenceran lebih lanjut dari larutan rekonstitusi 1 mg/mL dengan air steril untuk injeksi atau larutan infus karbohidrat, mis. dekstrosa tidak dianjurkan karena meningkatnya pembentukan kekeruhan dari larutan rekonstitusi. Actilyse tidak boleh dicampur dengan produk obat lain dalam botol infus yang sama (bahkan dengan heparin).
Larutan rekonstitusi hanya untuk sekali pakai. Larutan yang tidak digunakan harus dibuang.

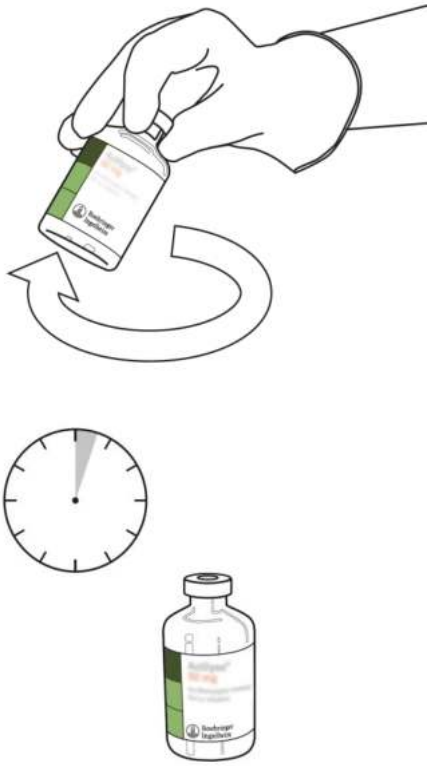
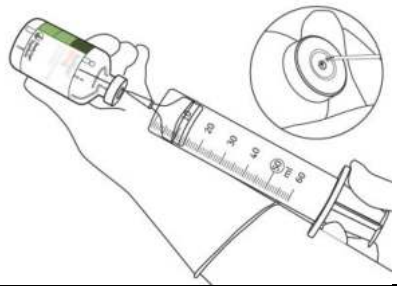
Instruksi untuk melakukan rekonstitusi Actilyse adalah sebagai berikut:

1	Rekonstitusi segera sebelum pemberian.	
2	Buka tutup pelindung pada kedua vial yang berisikan air steril dan serbuk kering ACTILYSE® dengan cara menjentikkannya dengan ibu jari.	

3	Usap tutup karet dari masing-masing vial dengan kapas alkohol.	
4	Lepaskan kanula transfer* dari pelindungnya. Jangan lakukan disinfeksi atau sterilisasi terhadap kanula transfer; kanula ini sudah steril. Buka satu penutup.	
5	Letakkan vial air steril dalam posisi berdiri pada permukaan yang stabil. Langsung dari atas, tusuk penutup karet secara vertikal di tengah-tengah stopper dengan kanula transfer, dengan cara menekan lembut tapi pasti, tanpa memutar.	 Sterile water for injection

6	Pegang vial air steril dan kanula transfer secara stabil dengan satu tangan menggunakan kedua sisi penutup. Lepaskan tutup yang tersisa di atas kanula tranfer.	
7	Pegang vial air steril dan kanula transfer secara stabil dengan satu tangan menggunakan kedua sisi penutup. Pegang vial yang berisi serbuk kering ACTILYSE® diatas kanula transfer secara vertikal dan posisi ujung kanula transfer tepat di tengah stopper. Tekan vial yang berisikan serbuk kering ke kanula transfer dari atas, menusuk stopper karet secara vertikal dan lembut tetapi pasti tanpa memutar.	  Actilyse (dry substance) ⇩ Sterile water for injection

8	Balikkan kedua vial dan biarkan airnya mengalir semua ke dalam serbuk kering.	  Sterile water for injection ⇩ Actilyse (dry substance)
9	Lepaskan vial yang telah kosong bersama dengan kanula transfernya. Keduanya dapat dibuang.	

10	Ambil vial yang berisi ACTILYSE® yang telah dilarutkan dan putar-putar perlahan untuk melarutkan serbuk yang tersisa, tetapi jangan dikocok, karena ini akan menghasilkan busa. Jika terdapat gelembung, biarkan larutan ini selama beberapa menit agar gelembung hilang.	
11	Larutan rekonstitusi ini mengandung ACTILYSE® 1mg/mL. Larutan ini jernih dan tidak berwarna hingga berwarna kuning pucat dan seharusnya tidak mengandung partikel apapun.	
12	Ambil jumlah yang dibutuhkan hanya dengan menggunakan jarum dan alat suntik. Jangan melubangi/ menusuk kanula transfer untuk menghindari kebocoran.	
13	Gunakan segera. Buanglah larutan tersisa yang tidak digunakan.	

Posologi dan metode pemberian

Infark miokard akut

Posologi

a) Regimen dosis 90 menit (dipercepat) untuk pasien dengan infark miokard akut, di mana pengobatan dapat dimulai dalam waktu 6 jam setelah onset gejala.

Pada pasien dengan berat badan ≥ 65 kg:

	Volume yang akan diberikan sesuai dengan konsentrasi alteplase
	1 mg/ml
15 mg sebagai bolus intravena, dan segera diikuti dengan	15 ml
50 mg sebagai infus intravena dengan kecepatan konstan selama 30 menit	50 ml

pertama, dan segera diikuti dengan	
35 mg sebagai infus intravena dengan kecepatan konstan selama 60 menit, hingga dosis total maksimum 100 mg	35 ml

Pada pasien dengan berat badan <65 kg total dosis harus harus disesuaikan dengan berat badan sesuai tabel berikut:

	Volume yang akan diberikan sesuai dengan konsentrasi alteplase
	1 mg/ml
15 mg sebagai bolus intravena, dan segera diikuti dengan	15 ml
0,75 mg/kg berat badan (bb) sebagai infus intravena dengan kecepatan konstan selama 30 menit pertama, kemudian segera diikuti dengan	0,75 ml/kg bb
0,5 mg/kg berat badan (bb) sebagai infus intravena dengan kecepatan konstan selama 60 menit	0,5 ml/kg bb

b) rejimen dosis 3 jam untuk pasien dengan infark miokard akut, dimana pengobatan dapat dimulai antara 6 dan 12 jam setelah dimulainya gejala onset.

Pada pasien dengan berat badan ≥ 65 kg:

	Volume yang akan diberikan sesuai dengan konsentrasi alteplase
	1 mg/ml
10 mg sebagai bolus intravena, dan segera diikuti dengan	10 ml
50 mg sebagai infus intravena dengan kecepatan konstan selama satu jam pertama, dan segera diikuti dengan	50 ml
40 mg sebagai infus intravena dengan kecepatan konstan selama 2 jam, hingga dosis total maksimum 100 mg	40 ml

Pada pasien dengan berat badan <65 kg:

	Volume yang akan diberikan sesuai dengan konsentrasi alteplase
	1 mg/ml
10 mg sebagai bolus intravena, dan segera diikuti dengan	10 ml
infus intravena dengan kecepatan konstan selama 3 jam hingga dosis total maksimum 1,5 mg/kg bb	1,5 ml/kg bb

Terapi ajuvan
Terapi tambahan antitrombotik direkomendasikan sesuai dengan pedoman internasional saat ini untuk pengelolaan pasien dengan infark miokard ST-elevasi;

Emboli paru masif akut
Posologi
Pada pasien dengan berat badan ≥ 65 kg:
Dosis total 100 mg alteplase harus diberikan dalam waktu 2 jam. Sebagian besar pengalaman tersedia dengan rejimen dosis berikut:

	Volume yang akan diberikan sesuai dengan konsentrasi alteplase
	1 mg/ml
10 mg sebagai bolus intravena selama 1 - 2 menit, dan segera diikuti dengan	10 ml
90 mg sebagai infus intravena dengan kecepatan konstan selama 2 jam hingga total dosis maksimum 100 mgtotal dose of 100 mg	90 ml

Pada pasien dengan berat badan < 65 kg:

	Volume yang akan diberikan sesuai dengan konsentrasi alteplase
	1 mg/ml
10 mg sebagai bolus intravena selama 1 - 2 menit, dan segera diikuti dengan	10 ml
infus intravena dengan kecepatan konstan lebih dari 2 jam hingga dosis total maksimum sebesar 1,5 mg/kg bb	1,5 ml/kg bb

Terapi penunjang
Setelah pengobatan dengan Actilyse, terapi heparin harus dimulai (atau dilanjutkan) bila nilai aPTT kurang dari dua kali batas atas normal. Infus harus disesuaikan untuk mempertahankan aPTT antara 50 - 70 detik (1,5 hingga 2,5 kali lipat dari nilai referensi).

Stroke iskemik akut
Pengobatan hanya boleh dilakukan di bawah tanggung jawab dan tindak lanjut dari seorang dokter yang terlatih dan berpengalaman dalam perawatan neurovaskular.

Pengobatan dengan Actilyse harus dimulai sedini mungkin dalam tempo 4,5 jam sejak terjadinya gejala. Di luar waktu 4,5 jam setelah terjadinya gejala stroke ada rasio risiko-manfaat yang negatif terkait dengan pemberian Actilyse dan karena itu tidak boleh diberikan.

Posologi
Dosis total yang direkomendasikan adalah 0,9 mg alteplase/kg berat badan (maksimum 90 mg) dimulai dengan 10% dari total dosis sebagai bolus intravena awal, kemudian segera diikuti dengan sisa dosis total yang diinfus secara intravena selama 60 menit.

TABEL DOSIS UNTUK STROKE ISKEMIK AKUT

Dengan menggunakan konsentrasi standar yang direkomendasikan 1 mg/ml, volume (ml) yang akan diberikan adalah sama dengan nilai dosis yang direkomendasikan (mg)			
Berat Badan (kg)	Total Dosis (mg)	Dosis Bolus (mg)	Dosis Infus * (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

* diberikan dalam konsentrasi 1mg/mL selama 60 menit sebagai infus dengan kecepatan konstan.

Terapi penunjang

Keamanan dan efektivitas rejimen ini dengan pemberian bersama heparin atau penghambat agregasi trombosit seperti asam asetilsalisilat dalam waktu 24 jam pertama setelah timbulnya gejala belum diselidiki secara memadai. Oleh karena itu, pemberian heparin intravena atau penghambat agregasi trombosit seperti asam asetilsalisilat harus dihindari dalam 24 jam pertama setelah pengobatan dengan Actilyse karena peningkatan risiko perdarahan. Jika heparin diperlukan untuk indikasi lain (mis. pencegahan trombosis vena dalam) dosis tidak boleh melebihi 10.000 IU per hari, dan diberikan secara subkutan.