1. NAME OF THE MEDICINAL PRODUCT

Actilyse 50 mg powder and solvent for solution for injection and infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with powder contains:
50 mg alteplase (corresponding to 29,000,000 IU), respectively

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.

Excipient(s) with known effect
Each 50 mg vial contains 5.0 mg polysorbate 80 (E 433).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion.

The powder is presented as a colourless to pale yellow lyophilizate cake. The reconstituted preparation is a clear and colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Thrombolytic treatment in acute myocardial infarction (AMI)
- 90 minutes (accelerated) dose regimen (see section 4.2): for patients in whom treatment can be started within 6 hours after symptom onset
- 3 hour dose regimen (see section 4.2): for patients in whom treatment can be started between 6 - 12 hours after symptom onset provided that the diagnosis has been clearly confirmed.

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

Thrombolytic treatment in acute massive pulmonary embolism with haemodynamic instability (PE)
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.

Thrombolytic treatment of acute ischaemic stroke (AIS) within 4.5 hours from last known well and after exclusion of intracranial haemorrhage.

4.2 Posology and method of administration

Actilyse should be prescribed by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use.

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

Acute myocardial infarction

Posology
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:

	Volume to be administered according to alteplase concentration	
	1 mg/ml	2 mg/ml
15 mg as an intravenous bolus, immediately followed by	15 ml	7.5 ml
50 mg as an intravenous constant rate infusion over the first 30 minutes, immediately followed by	50 ml	25 ml
35 mg as an intravenous constant rate infusion over 60 minutes, until the maximum total dose of 100 mg	35 ml	17.5 ml

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

	Volume to be administered according to alteplase concentration	
	1 mg/ml	2 mg/ml
15 mg as an intravenous bolus, immediately followed by	15 ml	7.5 ml
0.75 mg/kg body weight (bw) as an intravenous constant rate infusion over the first 30 minutes, immediately followed by	0.75 ml/kg bw	0.375 ml/kg bw
0.5 mg/kg body weight (bw) as an intravenous constant rate infusion over 60 minutes	0.5 ml/kg bw	0.25 ml/kg bw

b) 3 h 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:

	Volume to be administered according to alteplase concentration	
	1 mg/ml	2 mg/ml
10 mg as an intravenous bolus, immediately followed by	10 ml	5 ml
50 mg as an intravenous constant rate infusion over the first hour, immediately followed by	50 ml	25 ml
40 mg as an intravenous constant rate infusion over 2 hours, until the maximum total dose of 100 mg	40 ml	20 ml

In patients with a body weight < 65 kg:

	Volume to be administered according to alteplase concentration

	1 mg/ml	2 mg/ml
10 mg as an intravenous bolus, immediately followed by	10 ml	5 ml
an intravenous constant rate infusion over 3 hours up to a maximum total dose of 1.5 mg/kg bw	1.5 ml/kg bw	0.75 ml/kg bw

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

Method of administration
The reconstituted solution should be administered intravenously and is for immediate use.
2 mg vials of alteplase are not indicated for use in this indication. For instructions prior to reconstitution / administration, see section 6.6.

Acute massive pulmonary embolism

Posology
In patients with a body weight ≥ 65 kg:
A total dose of 100 mg of alteplase should be administered in 2 hours. Most experience is available with the following dose regimen:

	Volume to be administered according to alteplase concentration	
	1 mg/ml	2 mg/ml
10 mg as an intravenous bolus over 1 - 2 minutes, immediately followed by	10 ml	5 ml
90 mg as an intravenous constant rate infusion over 2 hours until the maximum total dose of 100 mg	90 ml	45 ml

In patients with a body weight < 65 kg:

	Volume to be administered according to alteplase concentration	
	1 mg/ml	2 mg/ml
10 mg as an intravenous bolus over 1 - 2 minutes, immediately followed by	10 ml	5 ml
an intravenous constant rate infusion over 2 hours up to a maximum total dose of 1.5 mg/kg bw	1.5 ml/kg bw	0.75 ml/kg bw

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).

Method of administration
The reconstituted solution should be administered intravenously and is for immediate use.
2 mg vials of alteplase are not indicated for use in this indication. For instructions prior to reconstitution / administration, see section 6.6.

Acute ischaemic stroke

Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care, see sections 4.3 and 4.4.

Treatment with Actilyse must be started for adults and adolescents ≥ 16 years of age (see sections 4.3 and 4.4) as early as possible and no later than 4.5 hours after last known well and after exclusion of intracranial haemorrhage by appropriate imaging techniques. The treatment effect is time-dependent; therefore, earlier treatment increases the probability of a favourable outcome. Beyond 4.5 hours after onset of stroke symptoms there is a negative benefit risk ratio associated with Actilyse administration and so it should not be administered (see section 5.1).

Posology

The recommended total dose is 0.9 mg alteplase/kg body weight (maximum of 90 mg) starting with 10% of the total dose as an initial intravenous bolus, immediately followed by the remainder of the total dose infused intravenously over 60 minutes.

DOSING TABLE FOR ACUTE ISCHAEMIC STROKE			
By using the recommended standard concentration of 1 mg/ml the volume (ml) to be administered is equal to the recommended dosing value (mg)			
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 1mg/mL over 60 min as a constant rate infusion.

Adjunctive therapy
Drugs affecting coagulation/platelet function
The safety and efficacy of this regimen with concomitant administration of heparin or platelet aggregation inhibitors such as acetylsalicylic acid within the first 24 hours after treatment with Actilyse have not been sufficiently investigated. 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.
2 mg vials of alteplase are not indicated for use in this indication. For instructions prior to reconstitution / administration, see section 6.6.

Paediatric population

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

4.3 Contraindications

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

Contraindications in acute myocardial infarction, acute massive pulmonary embolism and acute ischaemic stroke:

Actilyse is contraindicated in situations associated with a high risk of bleeding such as:
- significant bleeding disorder at present or within the past 6 months
- known haemorrhagic diathesis
- manifest or recent severe or dangerous bleeding
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- recent (less than 10 days) obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- severe uncontrolled arterial hypertension (see section 4.4)
- bacterial endocarditis, pericarditis
- acute pancreatitis
- active ulcerative gastrointestinal disease, oesophageal varices, known arterial-aneurysm and/or arterial/venous malformation
- 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 months.

Additional contraindications in acute myocardial infarction and acute massive pulmonary embolism:
- any known history of haemorrhagic stroke or stroke of unknown origin
- known history of ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months except current acute ischaemic stroke within 4.5 hours.
- patients receiving effective oral anticoagulant treatment (e.g. vitamin K antagonists with INR > 1.3) (see section 4.4).

Additional contraindications in acute ischaemic stroke:

- 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
- known history of or suspected intracranial haemorrhage
- evidence of intracranial haemorrhage (ICH) on the CT-scan
- symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal
- patients receiving effective anticoagulation (e.g. vitamin K antagonists with INR > 1. 7) (see section 4.4)
- 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^3
- systolic blood pressure > 185 mm Hg or diastolic BP > 110 mm Hg, or when BP cannot be reduced below these limits by careful management
- blood glucose < 50 mg/dL (see section 4.4) or > 400 mg/dL (< 2.8 mM or > 22.2 mM).

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

4.4 Special warnings and precautions for use

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

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

It is recommended that when Actilyse is administered, standard resuscitation equipment and pharmacotherapy is available in all circumstances.

Hypersensitivity
Immune-mediated hypersensitivity reactions associated with the administration of Actilyse can be caused by the active substance alteplase or any of the excipients. No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systematic experience with re-administration of Actilyse.
There is also a risk of hypersensitivity reactions mediated through a non-immunological mechanism.

Angio-oedema represents the most common hypersensitivity reaction reported with Actilyse. This risk may be enhanced in the indication acute ischaemic stroke and/or by concomitant treatment with ACE inhibitors (see section 4.5). Patients treated with Actilyse should be monitored for angio-oedema during and for up to 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 (see section 4.3) (see section 4.2 for AIS). 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.
If a potentially dangerous bleeding occurs, in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued and concomitant heparin administration should be terminated immediately. 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.

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

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
- prolonged (> 2 minutes) or traumatic cardiopulmonary resuscitation or cardiac massage
- patients receiving oral anticoagulant treatment: The use of Actilyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely confirmed by appropriate test(s) of anticoagulant activity for the product(s) concerned showing no clinically relevant activity on the coagulation system (e.g. INR≤ 1.3 (AMI and PE) or INR ≤ 1.7 (AIS) for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).

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

Paediatric population
As yet, there is only limited experience with the use of Actilyse in children and adolescents.
When Actilyse is considered for the treatment of acute ischaemic stroke in carefully selected adolescents ≥ 16 years of age the benefit should be weighed carefully against the risks on an individual basis and discussed with the patient and parent/guardian as appropriate. Adolescents ≥ 16 years of age should be treated according to the instruction in the label for the adult population after imaging by appropriate techniques to rule out stroke mimics and confirming arterial occlusion corresponding to the neurological deficit (see section 5.1).

Additional special warnings and precautions in acute myocardial infarction and acute massive pulmonary embolism:
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.

The expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with:

- systolic blood pressure > 160 mm Hg (see section 4.3)
- body weight < 50 kg
- advanced age, i.e. patients 75 years or older, which may increase the risk of intracerebral haemorrhage.

GPIIb/IIIa antagonists:

Concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

Additional special warnings and precautions in acute myocardial infarction

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

Additional special warnings and precautions in acute ischaemic stroke:

Thrombolytic treatment requires adequate monitoring. Treatment must be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care and the use of thrombolytic treatments, with the facilities to monitor that use. For the verification of treatment indication remote diagnostic measures may be considered as appropriate see section 4.1 and 4.2.

Special warnings / conditions with a decreased benefit/risk ratio:

Bleeding
Intracerebral haemorrhage represents the major adverse reaction in the treatment of acute ischaemic stroke (up to 15 % of patients without any increase of overall mortality and without any relevant increase in overall mortality and severe disability combined, i.e. modified Rankin scale [mRS] score of 5 and 6).
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:

- as time to treatment from onset of stroke symptoms increases, net clinical benefit decreases. Therefore, the administration of Actilyse should not be delayed.
- patients pre-treated with acetylsalicylic acid (ASA) may have a greater risk of intracerebral haemorrhage and/or mortality, particularly if Actilyse treatment is delayed.
- compared to younger patients, patients of advanced age (over 80 years) may have a somewhat poorer outcome independent of treatment. They are also more likely to have more severe strokes which are associated with a higher absolute risk of intracerebral haemorrhage when thrombolysed compared with milder strokes when thrombolysed or with non-thrombolysed patients. Although available data indicate that the net benefit of Actilyse in patients over 80 years is smaller compared with younger patients, Actilyse can be used in patients over 80 years on an individual benefit-risk basis (see section 5.1). Patients of advanced age should be selected very carefully taking into account both the general health and the neurological status.

Special groups at reduced benefit/risk ratio
The benefit/risk ratio of Actilyse administration should be thoroughly considered in AIS patients with the following conditions:

- the therapeutic benefit is reduced in patients that had a prior stroke (see also section 4.3) 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 section 4.3)
- patients with very severe stroke are at higher risk for intracerebral haemorrhage and death and should not be treated (see section 4.3)
- 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 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 bleedings increases, independently from treatment
- seizure at the onset of stroke (Thrombolytic therapy in these patients should only be considered when there is no suspicion of a stroke mimic or significant head trauma)

- in patients initially presenting with blood glucose < 50 mg/dL, thrombolysis may be considered after correction to normal blood glucose values, if the diagnosis of AIS persists (see section 4.3).

Blood pressure monitoring
Blood pressure (BP) monitoring during treatment administration and the first 24 hours after alteplase treatment is necessary; an intravenous antihypertensive therapy is recommended if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg.

Other special warnings
Reperfusion of the ischaemic area may induce cerebral oedema in the infarcted zone.
Due to an increased haemorrhagic risk, treatment with platelet aggregation inhibitors should not be initiated within the first 24 hours following thrombolysis with alteplase.

Actilyse contains polysorbate 80
This medicine contains 5.0 mg of polysorbate 80 in 50 mg vial. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Actilyse and medicinal products commonly administered in patients with acute myocardial infarction, acute massive pulmonary embolism or acute ischaemic stroke 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 (when administered prior to, during or after alteplase therapy). These products should be avoided in the first 24 hours after Actilyse treatment for acute ischaemic stroke. With regard to pre-treatment with these substances, see sections 4.2, 4.3, and 4.4.

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

Concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of alteplase in pregnant women. Nonclinical studies performed with alteplase in doses higher than human doses exhibited fetal immaturity and/or embryotoxicity, secondary to the known pharmacological activity of the drug. Alteplase is not considered to be teratogenic (see section 5.3).
In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk.

Breast-feeding
It is unknown whether alteplase is excreted into human milk and there is insufficient information on the excretion of alteplase in animal milk.
Caution should be exercised when Actilyse is used for a nursing woman and a decision must be made whether breast-feeding should be discontinued for the first 24 hours after use of Actilyse.

Fertility
Clinical data on fertility are not available for Actilyse. Nonclinical studies performed with alteplase showed no adverse effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The most frequent adverse reaction associated with Actilyse is bleeding in different forms resulting in a fall in haematocrit and/or haemoglobin values.

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1 000 to <1/100), Rare (≥1/10 000 to <1/1 000), Very rare (<1/10 000), Not known (cannot be estimated from the available data).

Except for intracerebral/intracranial haemorrhage as adverse reaction in the indication 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 adverse reaction 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.

Table 1 Adverse reactions in acute myocardial infarction, acute massive pulmonary embolism and acute ischaemic stroke

System Organ Class	**Adverse Reaction**
Haemorrhage	
very common	intracerebral haemorrhage represents the major adverse reaction in the treatment of acute ischaemic stroke all haemorrhages including those in this table, e.g. ICH and non-ICH
common	intracerebral haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage) in the treatment of acute myocardial infarction and acute massive pulmonary embolism pharyngeal haemorrhage gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage, gingival bleeding) ecchymosis urogenital haemorrhage (such as haematuria, haemorrhage urinary tract) injection site haemorrhage (puncture site haemorrhage, catheter site haematoma, catheter site haemorrhage)
uncommon	pulmonary haemorrhage (such as haemoptysis, hemothorax, respiratory tract haemorrhage) epistaxis ear haemorrhage

rare	eye haemorrhage pericardial haemorrhage retroperitoneal bleeding (such as retroperitoneal haematoma)
not known***	bleeding in parenchymatous organs (such as hepatic haemorrhage)
Immune system disorders	
rare	hypersensitivity reactions (e.g. rash, urticaria, bronchospasm, angio-oedema, hypotension, shock)*
very rare	serious anaphylaxis
Nervous system disorders	
very rare	events related to the nervous system (e.g. epileptic seizure, convulsion, aphasia, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression, psychosis) often in association with concurrent ischaemic or haemorrhagic cerebrovascular events
Cardiac disorders**	
very common	recurrent ischaemia / angina pectoris, hypotension and heart failure / pulmonary oedema,
common	cardiogenic shock, cardiac arrest and reinfarction
uncommon	reperfusion arrhythmias (such as arrhythmia, extrasystoles, AV block first degree to atrioventricular block complete, atrial fibrillation / flutter, bradycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia / fibrillation, electromechanical dissociation [EMD]) mitral regurgitation, pulmonary embolism, other systemic embolism / cerebral embolism, ventricular septal defect
Vascular disorders	
rare	Embolism which may lead to corresponding consequences in the organs concerned
Gastrointestinal disorders	
rare	nausea
not known***	vomiting
Investigations	
uncommon	blood pressure decreased
not known***	body temperature increased
Injury and poisoning and procedural complications	
not known***	fat embolism (cholesterol crystal embolisation), which may lead to corresponding consequences in the organs concerned
Surgical and medicinal procedures	
not known***	Blood transfusions (necessary)

* See sections 4.4 and 4.5

**Cardiac disorders

As with other thrombolytic agents, the events described above under the respective section have been reported as sequelae of myocardial infarction and / or thrombolytic administration. These cardiac events can be life-threatening and may lead to death.

***Frequency calculation

This adverse reaction has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than “rare” but might be lower. Precise frequency estimation is not possible as the adverse drug reaction did not occur in a clinical trial database of 8299 patients.

Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Symptoms
If the maximum recommended dose is exceeded the risk of intracranial bleeding increases.
The relative fibrin specificity notwithstanding, a clinically significant reduction in fibrinogen and other blood coagulation components may occur after overdosage.

Therapy
In most cases, it is sufficient to await the physiological regeneration of these factors after the Actilyse therapy has been terminated. If, however, severe bleeding results, the infusion of fresh frozen plasma is recommended and if necessary, synthetic antifibrinolytics may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, ATC code: B01AD02

Mechanism 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.

Pharmacodynamic effects
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 efficacy and safety
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 intravenous 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 subcutaneous or intravenous 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.

Acute myocardial infarction
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.

Acute massive 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.

Acute ischaemic stroke Patients
In two USA studies (NINDS A/B) a significant higher proportion of patients, had a favourable outcome with alteplase, compared to placebo (no or minimal disability). These findings were confirmed in the ECASS III trial (see paragraph below), after in the meantime two European studies and an additional USA study had failed to provide the respective evidence in settings essentially not compliant with the current EU product information.

The ECASS III trial was a placebo-controlled, double-blind trial conducted in patients with acute stroke in a time-window of 3 to 4.5 hours in Europe. Treatment administration in the ECASS III study was in line with the European SmPC for Actilyse in its stroke indication, except the upper end of the time of treatment window i.e. 4.5 hours. 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. A total of 821 patients (418 alteplase/403 placebo) were randomized. More patients achieved favourable outcome with alteplase (52.4%) vs. placebo (45.2%; odds ratio [OR] 1.34; 95% CI 1.02 - 1.76; P=0.038). The incidence of any ICH/SICH was higher with alteplase vs. placebo (any ICH 27.0% vs 17.6%, p=0.0012; 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). Subgroup results of ECASS III confirm that a longer OTT is associated with an increasing risk for mortality and symptomatic intracranial haemorrhage. The results of ECASS III show a positive net-clinical benefit for Actilyse in the 3 to 4.5 hour time window, while pooled data demonstrate that the net-clinical benefit is no longer favourable for alteplase in the time window beyond 4.5 hours.

The safety and efficacy of Actilyse for acute ischaemic stroke treatment up to 4.5 hours time *stroke onset time to start of treatment* (OTT) has been assessed by an ongoing registry (SITS-ISTR: The Safe Implementation of Thrombolysis in Stroke registry). In this observational study safety outcome data of 21.566 treated patients in the 0 to 3 hour time window were compared with data from 2.376 patients treated between 3 to 4.5 hours after onset of AIS. The incidence of symptomatic intracranial haemorrhage (according to the SITS-MOST definition) was found to be higher in the 3 to 4.5 hour time window (2.2%) as compared with the up to 3 hour time window (1.7%). Mortality rates at 3 months were similar comparing the 3 to 4.5 hour time window (12.0%) with the 0 to 3.0 hours time window (12.3%) with an unadjusted OR 0.97 (95% CI: 0.84-1.13, p=0.70) and an adjusted OR 1.26 (95% CI: 1.07-1.49, p=0.005. The SITS observational data support clinical trial evidence of *stroke onset time to start of treatment* (OTT) as an important predictor of outcome following acute stroke treatment with alteplase.

Elderly (> 80 years)
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 probability of a good stroke outcome (mRS 0 - 1 at day 90/180) was increased and was associated with a larger benefit when treated earlier for all age groups (p-value for interaction of 0.0203) and was independent of age.

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 1.11-3.13) and in 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).

Type 2 parenchymal haemorrhage within 7 days occurred in 231 (6.8%) of 3,391 patients assigned to alteplase versus 44 (1.3%) of 3,365 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).

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).

Paediatric population
Observational non-randomised and non-comparative data on stroke patients of 16 -17 years of age with confirmed alteplase treatment was obtained from SITS-ISTR (Safe Implementation of Treatments in Stroke - International Stroke Thrombolysis Register, an independent, international registry). Between 2003 and the end of 2017, a total of 25 paediatric patients with confirmed alteplase use within the age group of 16 – 17 years were collected in the SITS registry. The median dose of alteplase used in this age group was 0.9mg/kg (range: 0.83 - 0.99mg/kg). 23 of 25 patients initiated treatment within the 4.5h after stroke symptoms onset (19 by 3h; 4 by 3 - 4.5h; 1 by 5 – 5.5h; 1 case not reported). The weight ranged from 56 – 90 kg. Most patients presented with moderate or moderate to severe stroke with a median NIHSS of 9.0 (range 1 – 30) at baseline.
Day 90 mRS scores were available in 21/25 patients. At day 90, 14/21 patients had a mRS score of 0-1 (no symptoms or no significant disability) and 5 further patients had mRS = 2 (slight disability). This means that 19/21 (over 90%) of the patients had a favourable outcome at day 90 according to mRS. The remaining 2 patients had either a reported outcome of moderate severe disability (mRS=4; n=1), or death (mRS=6) within 7 days (n=1).
Four patients did not have a day 90 mRS score reported. The last available information showed that 2/4 patients had a mRS of 2 at day 7 and 2/4 patients reported a clear global improvement at day 7.
Safety data on adverse events for haemorrhages and oedema were also available in the registry. Of the 25 patients from age category 16 -17 years, none had symptomatic intracerebral haemorrhage (sICH, ICH bleeding type PH2). 5 cases developed cerebral oedema after alteplase treatment. 4/5 patients with cerebral oedema had either a reported day 90 mRS between 0 and 2 or showed a global improvement at day 7 post treatment. One patient had a mRS=4 (moderate severe disability) reported at day 90. None of the cases experienced a fatal outcome.
In summary, there were 25 reports from the SITS Register of patients between 16 and 17 years of age with acute ischaemic stroke who have been treated according to adult recommendations with alteplase. Although the small sample size precludes a statistical analysis, the overall results show a positive trend with the respective adult dose used in these patients. The data do not appear to show an increased risk of symptomatic intracerebral haemorrhage or oedema compared to adults.

5.2 Pharmacokinetic properties

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 ml/min.). Under physiological conditions, the major portion of alteplase in the circulation is

inhibitor-bound. Hepatic clearance of alteplase is not hindered by the presence of other proteins including alteplase inhibitors. Complexes of alteplase and its inhibitor are eliminated as free alteplase. The relevant plasma half-life $t_{1/2}$ alpha is 4-5 minutes. This means that after 20 minutes less than 10 % of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured.

5.3 Preclinical safety data

In subchronic toxicity studies in rats and marmosets no unexpected undesirable effects were found. No indications of a mutagenic potential were found in mutagenic tests.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Arginine
Phosphoric acid (E 338) (for pH-adjustment)
Polysorbate 80 (E 433)

Solvent:
Water for injections

6.2 Incompatibilities

The reconstituted solution may be diluted with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg alteplase per ml.

Further dilution, the use of water for injections for dilution 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 medicinal products neither in the same infusion vial nor the same catheter (not even with heparin).

6.3 Shelf life

Unopened vials
3 years for Actilyse 50 mg powder and solvent for solution for injection and infusion.

Reconstituted solution
The reconstituted solution has been demonstrated to be stable for 24 hours at 2 °C – 8 °C and for 8 hours at 25 °C.

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 to 8°C.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Do not store above 30 °C.

For storage conditions after reconsititution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:
50 ml sterilised glass vials, sealed with sterile siliconised grey butyl-type stoppers with aluminium/plastic flip-off caps.

Solvent:
For the 50 mg pack sizes, the water for injections is filled into either 50 ml vials, depending on the size of the powder vials. The water for injections vials are sealed with rubber stoppers and aluminium/plastic flip-off caps.

Transfer cannulas (included with pack sizes of 20 mg and 50 mg only)

Pack sizes:

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For reconstitution to a final concentration of 1 mg alteplase per ml the full volume of solvent provided should be transferred to the vial containing the Actilyse powder. To this purpose a transfer cannula is included with the 20 mg and 50 mg pack sizes, which is to be used. For the 10 mg vial a syringe should be used.

For reconstitution to a final concentration of 2 mg alteplase per ml only half of the solvent provided should be used (as per table below). In these cases always a syringe should be used to transfer the required amount of solvent to the vial containing the Actilyse powder.

Under aseptic conditions the content of an injection vial of Actilyse (10 mg or 20 mg or 50 mg) 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:

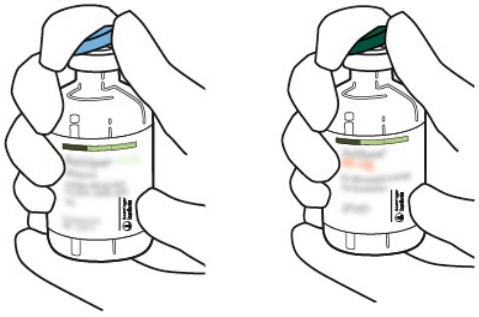
Actilyse dry substance	50 mg
(a) Volume of sterilised water for injections to be added to dry substance	50 mL
Final concentration:	1 mg alteplase/mL
(b) Volume of sterilised water for injections to be added to dry substance	25 mL
Final concentration:	2 mg alteplase/mL

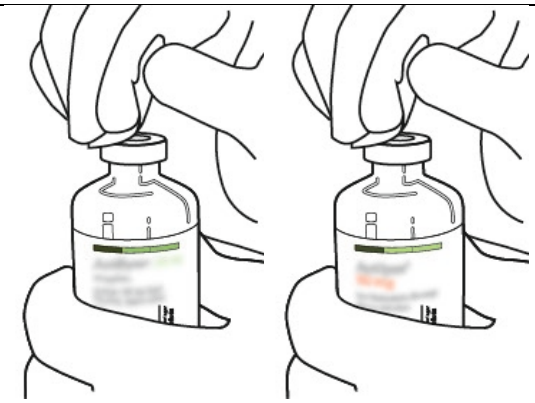
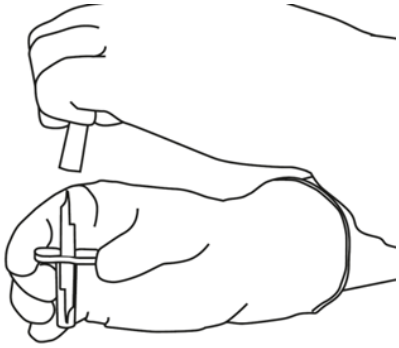
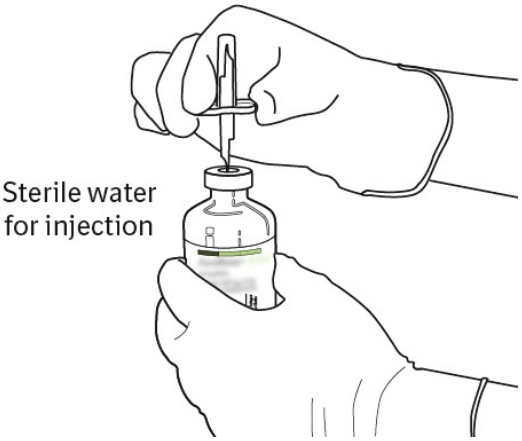
The reconstituted solution should then be administered intravenously. The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg/ml since the occurrence of turbidity of the reconstituted solution 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 medicinal products in the same infusion-vial (not even with heparin).

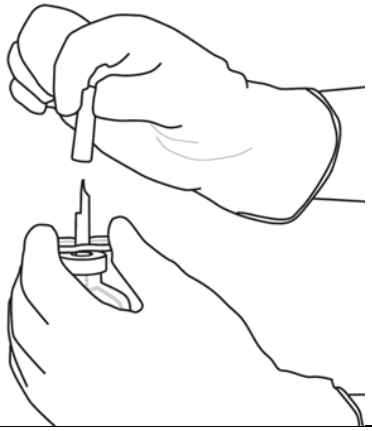
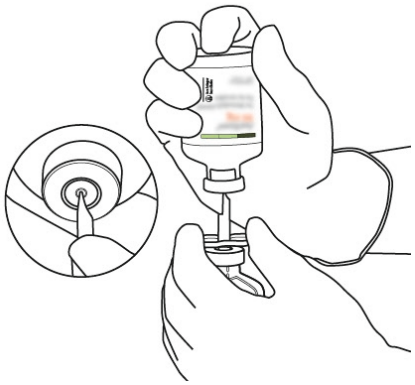
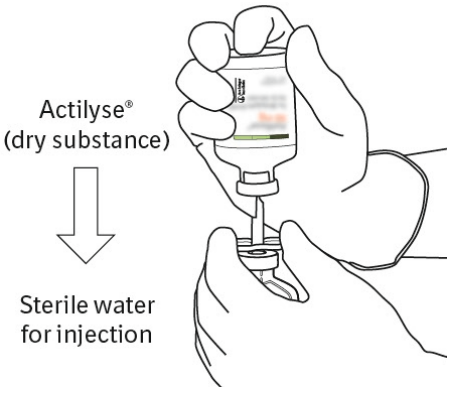
For incompatibilities see section 6.2.

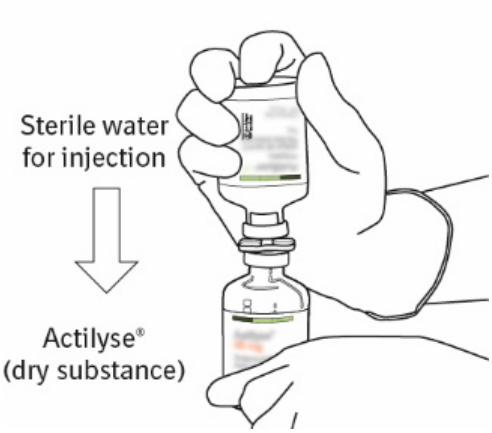
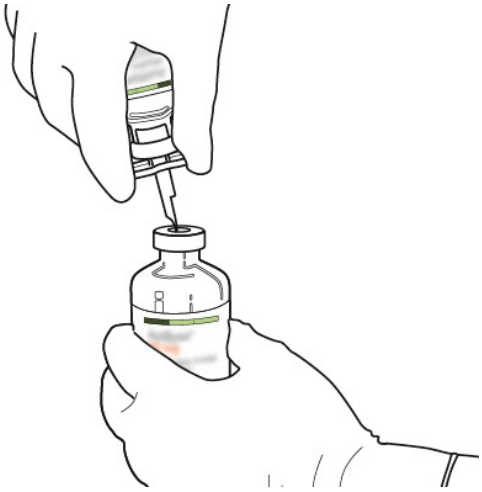
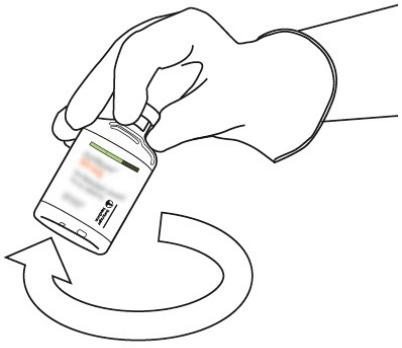
The reconstituted solution is for single use only. Any unused solution or waste material should be disposed in accordance with the local requirements.

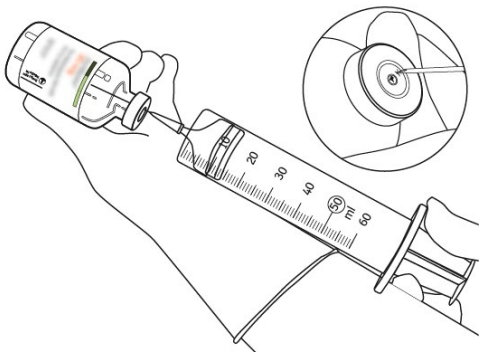
Instructions for reconstituting Actilyse

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 center with the transfer cannula, by pressing gently but firmly, without twisting.	
6	Hold the sterile water vial and the transfer cannula steady with one hand using the two side flaps. Remove the remaining cap on top of the transfer cannula.	

		
7	Hold the sterile water vial and the transfer cannula steady with one hand using the two side flaps. Hold the vial with Actilyse dry substance vertically above the transfer cannula and position the tip of the transfer cannula right in the center of the stopper. Push down the vial with the dry substance onto the transfer cannula from directly above, puncturing the rubber stopper vertically and gently but firmly without twisting.	 

8	Invert the two vials and allow the water to drain completely into the dry 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 alteplase. 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.)

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

A6-0592

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION