SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

Version: June, 2018

SUMMARY OF PRODUCT CHARACTERISTICS

Version: June, 2018

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Actilyse 10 mg powder and solvent for solution for injection and infusion
Actilyse 20 mg powder and solvent for solution for injection and infusion
Actilyse 50 mg powder and solvent for solution for injection and infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with powder contains:
10 mg alteplase (corresponding to 5,800,000 IU) or
20 mg alteplase (corresponding to 11,600,000 IU) or
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.

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

- 90 minutes (accelerated) dose regimen (see section 4.2): for patients in whom treatment can be started within 6 h after symptom onset
- 3 h dose regimen (see section 4.2): for patients in whom treatment can be started between 6 - 12 h 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
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.

Fibrinolytic treatment of acute ischaemic stroke
Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

4.2 Posology and method of administration

Actilyse should be given as soon 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:

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

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

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

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

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

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

The maximum dose of alteplase is 100 mg.

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.

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

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

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

Adjunctive therapy: After treatment with Actilyse heparin therapy should be initiated (or resumed) when aPTT values are less than twice the upper limit of normal. The infusion should be adjusted 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.
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.

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

Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms. 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).

Adjunctive therapy: The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of acetylsalicylic acid or intravenous heparin should be avoided in the first 24 hours after treatment with Actilyse. If heparin is required for other indications (e.g. prevention of deep vein thrombosis) the dose should not exceed 10,000 IU per day, administered subcutaneously.

Method of administration
The reconstituted solution should be administered intravenously.
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 16-17 years old is the same as for adults (see section 4.4 for recommendations on prior imaging techniques to be used).

4.3 Contraindications

Generally, in all indications Actilyse should not be administered to patients with known hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients listed in section 6.1.

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

Actilyse is contraindicated in cases where there is a high risk of haemorrhage such as:

- significant bleeding disorder at present or within the past 6 months
- known haemorrhagic diathesis
- patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (see section 4.4)
- manifest or recent severe or dangerous bleeding
- known history of or suspected intracranial haemorrhage
- suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- severe uncontrolled arterial hypertension
- bacterial endocarditis, pericarditis
- acute pancreatitis
- documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations
- neoplasm with increased bleeding risk
- severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- major surgery or significant trauma in past 3 months.

Additional contraindications in acute myocardial infarction:

- 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.

Additional contraindications in 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.

Additional contraindications in acute ischaemic stroke:

- symptoms of ischaemic attack beginning more than 4.5 hours prior to infusion start or symptoms for which the onset time is unknown and could potentially be more than 4.5 hours ago (see section 5.1)
- minor neurological deficit or symptoms rapidly improving before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques
- seizure at onset of stroke
- evidence of intracranial haemorrhage (ICH) on the CT-scan
- symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal
- administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory

- patients with any history of prior stroke and concomitant diabetes
- prior stroke within the last 3 months
- platelet count of below 100,000/mm^3
- systolic blood pressure > 185 mm Hg or diastolic BP > 110 mm Hg, or aggressive management (intravenous pharmacotherapy) necessary to reduce BP to these limits
- blood glucose < 50 mg/dl or > 400 mg/dl (< 2.8mM or > 22.2mM).

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

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

Thrombolytic/fibrinolytic treatment requires adequate monitoring. Actilyse should only be used under the responsibility and follow-up of physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use. 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, gentamicin (a trace residue from the manufacturing process), any of the excipients, or the stopper of the glass vial with Actilyse powder which contains natural rubber (a derivative of latex). 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 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.

Haemorrhages
If a potentially dangerous haemorrhage occurs, in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued. In general, however, it is not necessary to replace the coagulation factors because of the short half-life and the minimal effect on the systemic coagulation factors. Most patients who have bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement, and manual pressure applied to an incompetent vessel. Protamine should be considered if heparin has been administered within 4 hours of the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative.

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

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

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

The use of rigid catheters should be avoided.

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 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).

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).

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

Additional special warnings and precautions in acute ischaemic stroke:

Special precautions for use:
Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care. For the verification of treatment indication remote diagnostic measures may be considered as appropriate (see section 4.1).

Special warnings / conditions with a decreased benefit/risk ratio:
Compared to other indications patients with acute ischaemic stroke treated with Actilyse have a markedly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:

- all situations listed in section 4.3. and in general all situations involving a high risk of haemorrhage
- small asymptomatic aneurysms of the cerebral vessels
- 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 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. 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.

- 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 increasing age, increasing stroke severity and increased levels of blood glucose on admission while the likelihood of severe disability and death or relevant intracranial bleedings increases, independently from treatment. Patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 50 mg/dl or > 400 mg/dl (<2.8 mM or > 22.2mM) at baseline should not be treated with Actilyse (see section 4.3).

Blood pressure monitoring
Blood pressure (BP) monitoring during treatment administration and up to 24 hours seems justified; an intravenous antihypertensive therapy is also 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

The risk of haemorrhage is increased if coumarine derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or active substances which interfere with coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse) (see section 4.3).

Concomitant treatment with ACE inhibitors may enhance the risk of suffering 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 limited amount of data from the use of Actilyse 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 not known if alteplase is excreted into human milk.

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 myocardial infarction, there is no medical reason to assume that the qualitative and quantitative adverse reaction profile of Actilyse in the indications pulmonary embolism and acute ischaemic stroke is different from the profile in the indication 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 (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. mRS of 5 and 6). bleeding from damaged blood vessels (such as haematoma)
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 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 via the national reporting system listed in Appendix V.

4.9 Overdose

The relative fibrin specificity notwithstanding, a clinical significant reduction in fibrinogen and other blood coagulation components may occur after overdosage. In most cases, it is sufficient to await the physiological regeneration of these factors after the Actilyse therapy has been terminated. If, however, severe bleeding results, the infusion of fresh frozen plasma 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.). 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 (for pH-adjustment)
Polysorbate 80

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

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 25 °C.

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

6.5 Nature and contents of container

Powder:
10 ml, 20 ml or 50 ml sterilised glass vials, sealed with sterile siliconised grey butyl-type stoppers with aluminium/plastic flip-off caps.

Solvent:
For the 10 mg, 20 mg and 50 mg presentations, the water for injections is filled into either 10 ml, 20 ml or 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 presentations of 20 mg and 50 mg only)

Presentations:

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

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

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 presentations 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 presentations, which is to be used. For the 10 mg presentation 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:

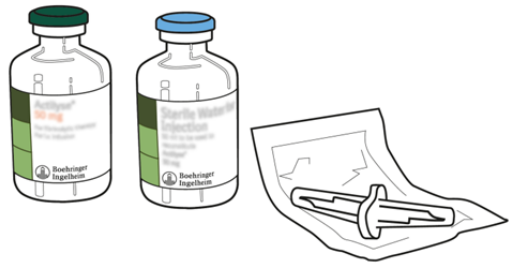
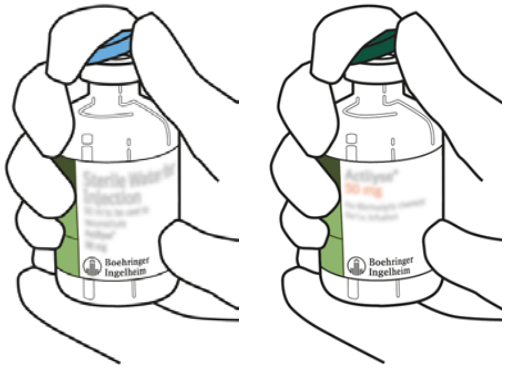
Actilyse dry substance	10 mg	20 mg	50 mg
(a) Volume of sterilised water for injections to be added to dry substance	10 mL	20 mL	50 mL
Final concentration:	1 mg alteplase/mL	1 mg alteplase/mL	1 mg alteplase/mL
(b) Volume of sterilised water for injections to be added to dry substance	5 mL	10 mL	25 mL
Final concentration:	2 mg alteplase/mL	2 mg alteplase/mL	2 mg alteplase/mL

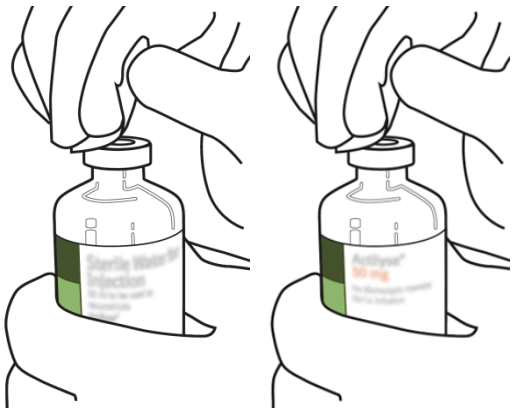
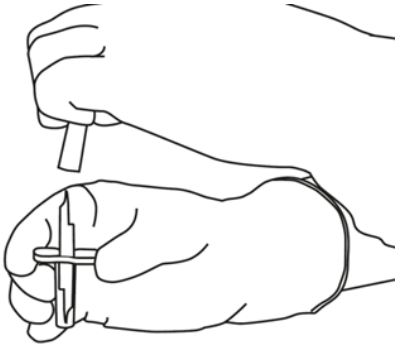
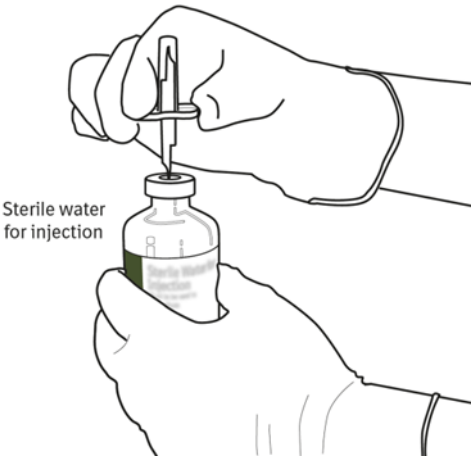
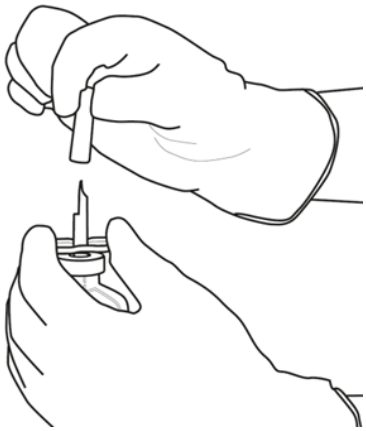
The reconstituted solution should then be administered intravenously. The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg/ml. A further dilution of the 1 mg/mL reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not recommended. Actilyse should not be mixed with other medicinal products in the same infusion-vial (not even with heparin).

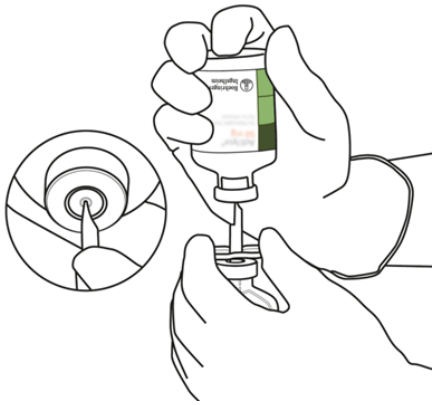
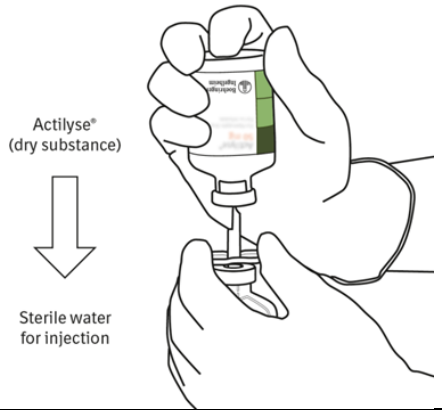
For incompatibilities see section 6.2.

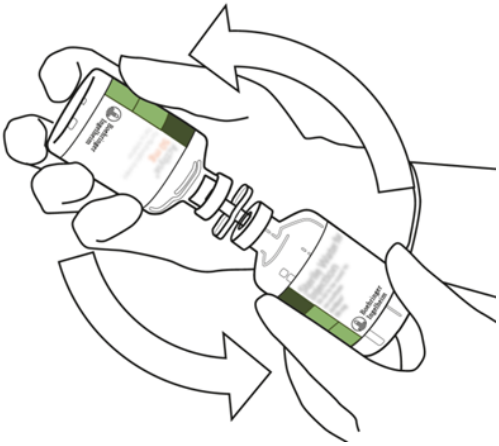
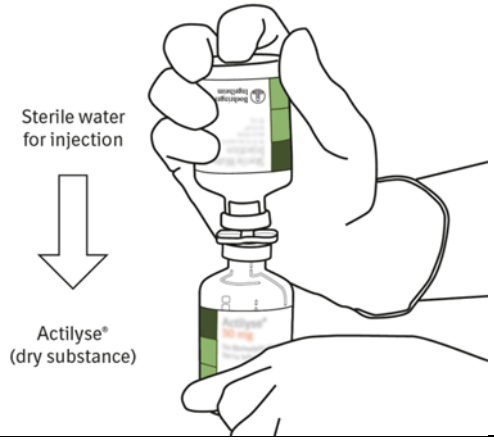
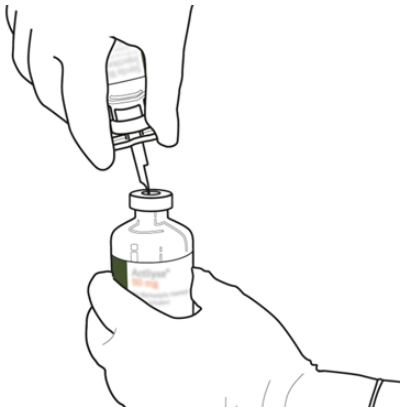
The reconstituted solution is for single use only. Any unused solution or waste material should be disposed in accordance with the local requirements.

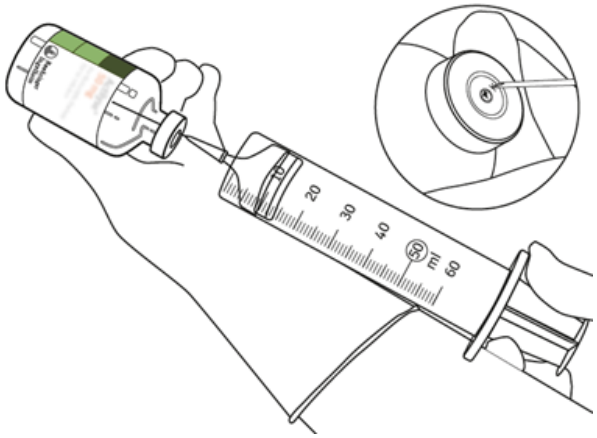
Instructions for reconstituting Actilyse

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 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 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 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (10 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]

Actilyse 10 mg powder and solvent for solution for injection and infusion
alteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg alteplase (corresponding to 5,800,000 IU).

3. LIST OF EXCIPIENTS

Arginine, phosphoric acid and polysorbate 80.
The rubber stopper of the packaging material contains natural rubber (latex).

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with 10 mg alteplase
1 solvent vial with 10 ml water for injections

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
For shelf life and storage of the reconstituted solution read the package leaflet.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION AND INFUSION (10 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

[To be completed nationally]

Actilyse 10 mg powder for solution for injection and infusion.
alteplase

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR SOLVENT (10 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Actilyse 10 mg

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml water for injections

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (20 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]

Actilyse 20 mg powder and solvent for solution for injection and infusion
alteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg alteplase (corresponding to 11,600,000 IU).

3. LIST OF EXCIPIENTS

Arginine, phosphoric acid and polysorbate 80.
The rubber stopper of the packaging material contains natural rubber (latex).

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with 20 mg alteplase
1 solvent vial with 20 ml water for injections
1 transfer cannula

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
For shelf life and storage of the reconstituted solution read the package leaflet.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION AND INFUSION (20 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Actilyse 20 mg powder for solution for injection and infusion
alteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

20 mg (11,6 MIU) alteplase.

3. LIST OF EXCIPIENTS

Arginine, phosphoric acid and polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL FOR SOLVENT (20 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Actilyse 20 mg

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 ml water for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (50 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Actilyse 50 mg powder and solvent for solution for injection and infusion
alteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg alteplase (corresponding to 29,000,000 IU).

3. LIST OF EXCIPIENTS

Arginine, phosphoric acid and polysorbate 80.
The rubber stopper of the packaging material contains natural rubber (latex).

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with 50 mg alteplase
1 solvent vial with 50 ml water for injections
1 transfer cannula

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
For shelf life and storage of the reconstituted solution read the package leaflet.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL FOR POWDER FOR SOLUTION FOR INJECTION AND INFUSION (50 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Actilyse 50 mg powder for solution for injection and infusion
alteplase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

50 mg (29 MIU) alteplase.

3. LIST OF EXCIPIENTS

Arginine, phosphoric acid and polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL FOR SOLVENT (50 MG PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Actilyse 50 mg

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

50 ml water for injections

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Justification for not including Braille accepted>

PACKAGE LEAFLET

Package leaflet: Information for the user

[To be completed nationally]

Actilyse 10 mg powder and solvent for solution for injection and infusion
Actilyse 20 mg powder and solvent for solution for injection and infusion
Actilyse 50 mg powder and solvent for solution for injection and infusion

Alteplase

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Actilyse is and what it is used for

The active substance in Actilyse is alteplase. It belongs to a group of medicines called thrombolytic agents. These medicines act by dissolving blood clots that have formed in blood vessels.

Actilyse 10, 20 or 50 mg are used to treat a number of conditions caused by blood clots forming within blood vessels, including:
- heart attack caused by blood clots in the arteries of the heart (acute myocardial infarction)
- blood clots in the arteries of the lungs (acute massive pulmonary embolism)
- stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke).

2. What you need to know before you receive Actilyse

You should not receive Actilyse
- if you are allergic (hypersensitive) to the active substance alteplase, to gentamicin (a trace residue from the manufacturing process), to natural rubber (also called latex which is part of the packaging material) or to any of the other ingredients of this medicine (listed in section 6).
- if you have, or have recently had, an illness that increases your risk of bleeding, including:
  - a bleeding disorder or tendency to bleed
  - a severe or dangerous bleed in any part of the body
  - bleeding within the brain or skull
  - uncontrolled, very high blood pressure
  - bacterial infection or inflammation of the heart (endocarditis), or inflammation of the membranes around the heart (pericarditis)
  - inflammation of the pancreas (acute pancreatitis)
  - gastric ulcer or ulcers in the gut
  - varicose veins in the gullet (oesophageal varices)
  - abnormalities of the blood vessels, such as a localised swelling of an artery (aneurysm)
  - certain tumours
  - severe liver disease

- if you are taking a medicine used to “thin” the blood (oral anticoagulants), unless appropriate tests confirmed no clinically relevant activity of such medicine
- if you have ever had surgery to your brain or spine
- if you have had major surgery or significant injury in the past 3 months
- if you had a recent puncture of a major blood vessel
- if you have been given external heart massage in the past 10 days
- if you have had a baby in the past 10 days

Your doctor will also not use Actilyse for the treatment of heart attacks or blood clots in the arteries of the lungs
- if you have or have ever had a stroke caused by bleeding in the brain (haemorrhagic stroke)
- if you have or have ever had a stroke of unknown cause
- if you have recently (in the past 6 months) had a stroke caused by a blood clot in an artery of the brain (ischaemic stroke), unless this is the stroke you are about to be treated for

In addition your doctor will not use Actilyse for the treatment of a stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke)
- if the symptoms of your stroke began more than 4.5 hours ago or if it may be possible that the symptoms began more than 4.5 hours ago, because you do not know when they began
- if your stroke is causing only very mild symptoms
- if there are signs of bleeding in the brain
- if you have had a stroke within the last three months
- if the symptoms are rapidly improving before receiving Actilyse
- if you have a very severe stroke
- if you had cramps (convulsions) when your stroke started
- if your thromboplastin time (a blood test to see how well your blood clots) is abnormal. This test can be abnormal if you have received heparin (a medicine used to “thin” the blood) within the previous 48 hours.
- if you are diabetic and have ever had a stroke before
- if the number of blood platelets (thrombocytes) in your blood is very low
- if you have a very high blood pressure (above 185/110) which can only be reduced by injection of medicines
- if the amount of sugar (glucose) in your blood is very low (under 50 mg/dl)
- if the amount of sugar (glucose) in your blood is very high (over 400 mg/dl)
- if you are under 16 years of age. (For adolescents of 16 years of age or older see section “Your doctor will take special care with Actilyse”.)

Your doctor will take special care with Actilyse
- if you have had any allergic reaction other than a sudden life-threatening allergic reaction (severe hypersensitivity) to the active substance alteplase, to gentamicin (a trace residue from the manufacturing process), to natural rubber (also called latex which is part of the packaging material) or to any of the other ingredients of this medicine (listed in section 6).
- if you have or have recently had any other conditions that increase your risk of bleeding, such as:
  - small injury
  - biopsy (a procedure for obtaining a tissue specimen)
  - puncture of major vessels
  - intramuscular injection
  - external heart massage
- if you have ever received Actilyse before.
- if you are over 65 years of age.
- if you are over 80 years of age, you may have a poorer outcome regardless of treatment with Actilyse. However, in general the benefit-risk of Actilyse in patients over 80 years is positive and age alone is not a barrier to treatment with Actilyse.
- if you are an adolescent of 16 years of age or older the benefit will be weighed carefully against the risks on an individual basis for the treatment of acute ischaemic stroke.

Other medicines and Actilyse
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important that you tell your doctor if you are taking or have recently taken:

- any medicines which are used to "thin " the blood, including:
  - acetylsalicylic acid
  - warfarin
  - coumarin
  - heparin
- certain medicines used to treat high blood pressure (ACE inhibitors).

Pregnancy, breast-feeding and fertility
Ask your doctor for advice before taking any medicine. Your doctor will only give you Actilyse if the possible benefit outweighs the possible risk to your baby.

Actilyse may contain gentamicin as trace residue from the manufacturing process; the packaging contains natural rubber (latex).

3. How is Actilyse administered

Actilyse will be prepared and administered to you by your doctor or by a health care professional. It is not for self-administration.

Treatment with Actilyse should be initiated as soon as possible after the start of your symptoms.

There are three different conditions for which this medicine can be given:

Heart attack (myocardial infarction)
The dose you are given depends on your body weight. The maximum dose of Actilyse is 100 mg but will be lower if you weigh less than 65 kg.
It can be administered in two different ways:

a) The 90 minute form of administration, for patients treated within 6 hours after start of their symptoms. This consists of:

- an initial injection of part of the dose of Actilyse into a vein
- infusions of the remainder of the dose over the following 90 minutes.

b) The 3 hour form of administration, for patients treated 6 to 12 hours after start of their symptoms. This consists of:

- an initial injection of part of the dose of Actilyse into a vein
- infusions of the remainder of the dose over the following 3 hours.

In addition to Actilyse your doctor will give you another medicine to stop the blood clotting. This will be given as soon as possible after your chest pain starts.

Blood clots in the arteries of the lungs (pulmonary embolism)
The dose you are given depends on your body weight. The maximum dose of Actilyse is 100 mg but will be lower if you weigh less than 65 kg.
The medicine is usually given as:

- an initial injection of part of the dose into a vein
- an infusion of the remainder of the dose over the following 2 hours.

After the treatment with Actilyse, your doctor will start (or resume) therapy with heparin (a medicine to "thin" the blood).

Stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke)
Actilyse must be given within 4.5 hours of the first symptoms. The earlier you receive Actilyse, the more you can benefit from the treatment and the less likely are harmful side effects to occur.The dose you are given depends on your body weight. The maximum dose of this medicine is 90 mg but will be lower if you weigh less than 100 kg. Actilyse is given as:

- an initial injection of part of the dose into a vein
- an infusion of the remainder of the dose over the following 60 minutes.

You should not take acetylsalicylic acid for the first 24 hours after your treatment with Actilyse for a stroke. Your doctor may give you an injection with heparin if this is necessary.

If you have any further questions on the use of Actilyse, ask your doctor or health care professional.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects described below have been experienced by people given Actilyse:

Very common (occurs in more than 1 in 10 patients receiving the medicine)

- heart failure – treatment cessation may be necessary
- bleeding in the brain (cerebral haemorrhage) after the treatment of a stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke) – treatment cessation may be necessary
- fluid on the lungs (pulmonary oedema)
- bleeding of the damaged blood vessel (such as haematoma) low blood pressure (hypotension)
- chest pain (angina pectoris)

Common (occurs in less than 1 in 10 patients receiving the medicine)

- further heart attack
- bleeding in the brain (cerebral haemorrhage) after the treatment of heart attacks (myocardial infarction) – treatment cessation may be necessary
- cessation of heartbeat (cardiac arrest) – treatment cessation may be necessary
- shock (a very low blood pressure) due to heart failure – treatment cessation may be necessary
- bleeding in the throat
- bleeding in the stomach or gut, including vomiting blood (haematemesis) or blood in the stools (melanea or rectal haemorrhage), bleeding of the gums
- bleeding into the body tissues causing purplish bruising (ecchymosis)
- bleeding from the urinary tract or the reproductive organs, which may lead to blood in your urine (haematuria)
- bleeding or bruising (haematoma) where the injection is given

Uncommon (occurs in less than 1 in 100 patients receiving the medicine)

- lung-related bleeding, such as blood stained phlegm (haemoptysis) or bleeding in the respiratory tract – treatment cessation may be necessary
- nosebleeds (epistaxis)
- irregular heart beat after the blood supply to the heart has been restored
- damage to the heart valves (mitral regurgitation) or to the wall dividing the heart chambers (ventricular septal defect) – treatment cessation may be necessary
- Sudden blocking of an artery in the lungs (pulmonary embolsim), the brain (cerebral embolism) and all other areas of the body (systemic embolism)
- bleeding from the ear
- blood pressure decreased

Rare (occurs in less than 1 in 1,000 patients receiving the medicine)

- bleeding into the membranous sac surrounding the heart (haemopericardium) – treatment cessation may be necessary
- internal bleeding into the back part of the abdomen (retroperitoneal bleeding) – treatment cessation may be necessary
- formation of blood clots in the blood vessels which can travel to other organs in the body (embolism). The symptoms will depend on the organ affected.
- allergic reactions, e.g. hives (urticaria) and rash, difficulty breathing up to asthma (bronchospasm), fluid under the skin and mucose membrane (angioedema), low blood pressure or shock – treatment cessation may be necessary
- bleeding in the eyes (eye haemorrhage)
- uneasiness of the stomach (nausea)

Very rare (occurs in less than 1 in 10,000 patients receiving the medicine)
- serious allergic reaction (e.g. life-threatening anaphylaxis) – treatment cessation may be necessary
- events which affect the nervous system such as:
  - cramps (convulsions, fits)
  - speech problems
  - confusion or delirium (very severe confusion)
  - anxiety accompanied by restlessness (agitation)
  - depression
  - altered thinking (psychosis)

  These disorders often occur in association with a stroke caused by a blood clot or bleeding in the brain.

Not known (frequency cannot be estimated from available data)
- bleeding in internal organs, e.g. bleeding in the liver (hepatic haemorrhage) – treatment cessation may be necessary
- formation of cholesterol crystal clots which can travel to other organs in the body (cholesterol crystal embolisation). The symptoms will depend on the organ affected – treatment cessation may be necessary
- bleeding which necessitates a blood transfusion
- vomiting
- body temperature increased (fever)

Death or permanent disability may occur following bleeding in the brain or other serious bleeding events.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Actilyse

Normally you will not be asked to store Actilyse as it will be given to you by your doctor.

Keep this medicine out of the sight and reach of children.

Do not store above 25°C. Store in the original package in order to protect from light.

Actilyse should not be used after the expiry date which is stated on the vial label and the carton. The expiry date refers to the last day of that month.

Chemical and physical in-use stability

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

6. Contents of the pack and other information

What Actilyse contains

- The active substance is alteplase. Each vial contains 10 mg (corresponding to 5,800,000 IU), 20 mg (corresponding to 11,600,000 IU) or 50 mg (corresponding to 29,000,000 IU) alteplase. The other ingredients are arginine, phosphoric acid (for pH-adjustment) and polysorbate 80.
- The solvent is water for injections.
- The rubber stopper of the packaging material contains natural rubber (latex).

What Actilyse looks like and contents of the pack

Actilyse is a powder and solvent for solution for injection and infusion.
Each pack contains one vial with powder and one vial with the solvent.

Actilyse is available in the following presentations:

- One vial of powder with 10 mg alteplase and one vial with 10 ml solvent.
- One vial of powder with 20 mg alteplase, one vial with 20 ml solvent and one transfer cannula.
- One vial of powder with 50 mg alteplase, one vial with 50 ml solvent and one transfer cannula.

Not all presentations may be marketed.

Marketing Authorisation Holder

<[To be completed nationally]>

Manufacturer
Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach/Riss
Germany

This leaflet was last revised in {MM/YYYY}.

The following information is intended for healthcare professionals only:

2 mg vials of alteplase are not indicated for use in the indications acute myocardial infarction, acute massive pulmonary embolism or acute ischaemic stroke (due to risk of massive under dosing). Only 10, 20 or 50 mg vials are indicated for use in these indications.

Reconstitution

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 presentations, 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:

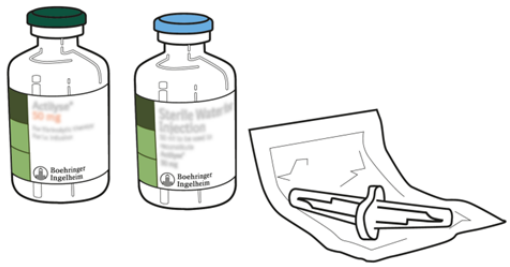
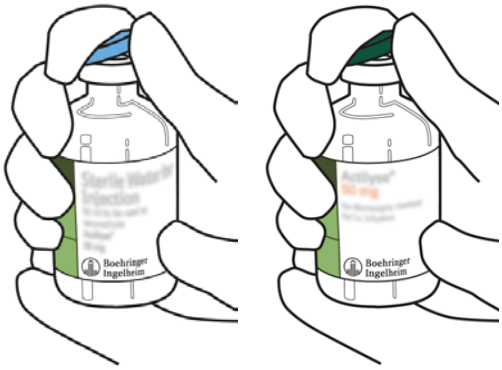
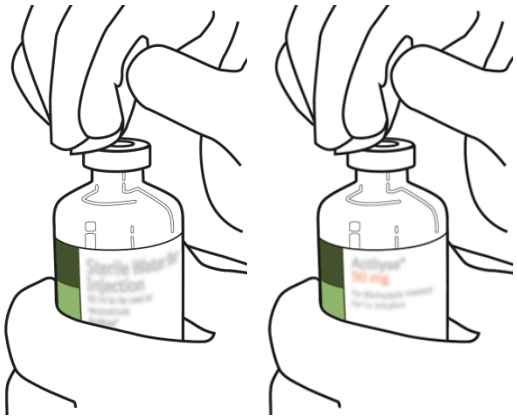
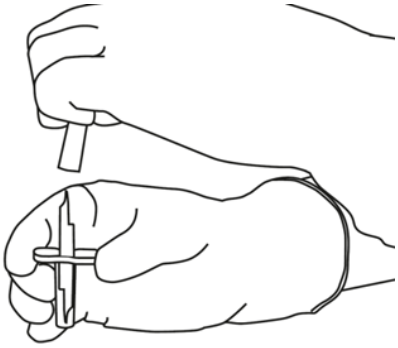
Actilyse dry substance	10 mg	20 mg	50 mg
a) Volume of sterilised water for injections to be added to dry substance	10 mL	20 mL	50 mL
Final concentration:	1 mg alteplase/mL	1 mg alteplase/mL	1 mg alteplase/mL
(b) Volume of sterilised water for injections to be added to dry substance	5 mL	10 mL	25 mL
Final concentration:	2 mg alteplase/mL	2 mg alteplase/mL	2 mg alteplase/mL

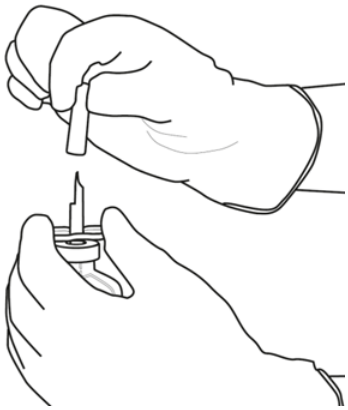
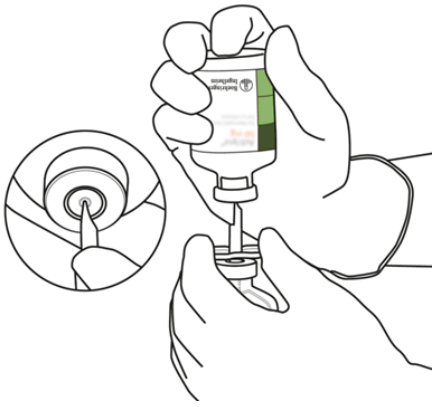
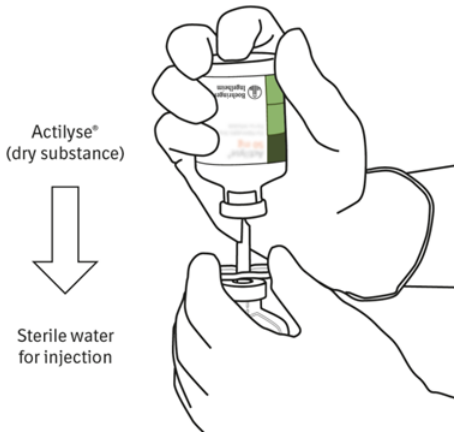
The reconstituted solution should then be administered intravenously. The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg/ml. A further dilution of the 1mg/mL reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not recommended. Actilyse should not be mixed with other medicinal products in the same infusion-vial (not even with heparin).

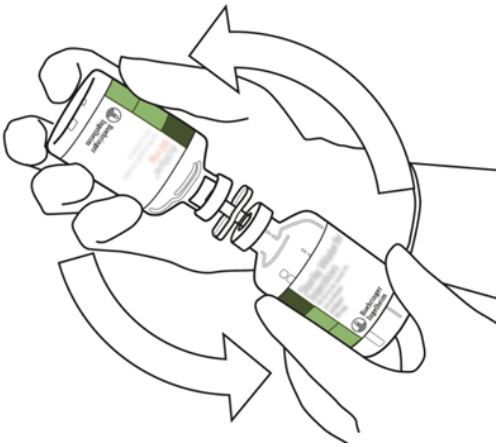
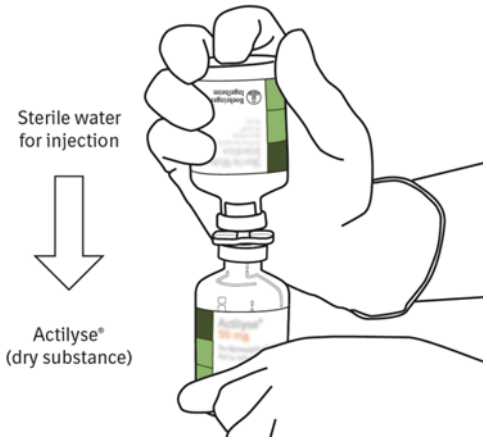
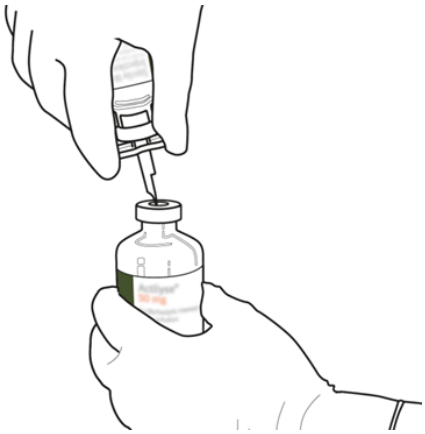
For storage conditions, please see section 5 of this leaflet.

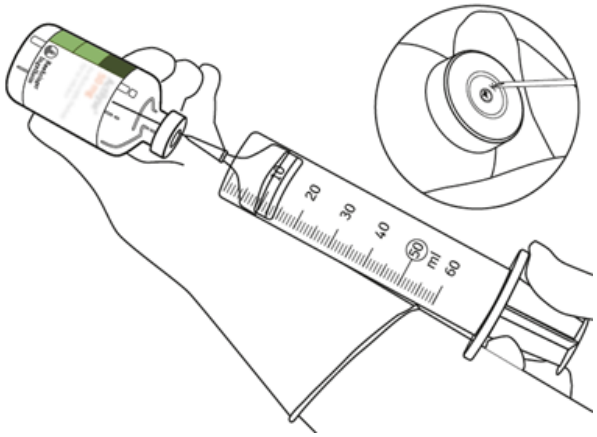
The reconstituted solution is for single use only. Any unused solution should be discarded.

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 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 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 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.)

Posology and method of administration

Acute Myocardial infarction

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

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

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

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

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

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

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

The maximum dose of alteplase is 100 mg.

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.
2 mg vials of alteplase are not indicated for use in this indication.

Acute massive pulmonary embolism

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

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

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

Adjunctive therapy: After treatment with Actilyse heparin therapy should be initiated (or resumed) when aPTT values are less than twice the upper limit of normal. The infusion should be adjusted 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.
2 mg vials of alteplase are not indicated for use in this indication.

Acute ischaemic stroke
Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care, see SmPC sections 4.3 contraindications and 4.4 special warnings/ precautions for use.

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

Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms. 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 SmPC section 5.1).

Adjunctive therapy: The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of acetylsalicylic acid or intravenous heparin should be avoided in the first 24 hours after treatment with Actilyse. If heparin is required for other indications (e.g. prevention of deep vein thrombosis) the dose should not exceed 10,000 IU per day, administered subcutaneously.

Method of administration
The reconstituted solution should be administered intravenously.
2 mg vials of alteplase are not indicated for use in this indication.

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 SmPC section 4.3). The dose for adolescents 16-17 years old is the same as for adults (see SmPC section 4.4 for recommendations on prior imaging techniques to be used).

Adolescents of 16 years of age or older 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.