Package leaflet: Information for the user

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

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 alteplase 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 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
If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor for advice. Your doctor will only give you Actilyse if the possible benefit outweighs the possible risk to your baby.

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 (acute 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 (acute massive 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. Your treatment may be stopped by your doctor if any of the following side effects occur:

- 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)
- cessation of heartbeat (cardiac arrest)
- shock (a very low blood pressure) due to heart failure
- bleeding in the brain (cerebral haemorrhage) after the treatment of heart attacks (myocardial infarction)
- lung-related bleeding, such as blood stained phlegm (haemoptysis) or bleeding in the respiratory tract
- bleeding into the membranous sac surrounding the heart (haemopericardium)
- internal bleeding into the back part of the abdomen (retroperitoneal bleeding)
- damage to the heart valves (mitral regurgitation) or to the wall dividing the heart chambers (ventricular septal defect)
- bleeding in internal organs, e.g. bleeding in the liver (hepatic haemorrhage)
- 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
- 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
- serious allergic reaction (e.g. life-threatening anaphylaxis)
- heart failure

The following are other possible side effects that may cause your doctor to stop your treatment but, this will depend on how severe the side effects are:

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

- 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 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)

- nosebleeds (epistaxis)
- irregular heart beat after the blood supply to the heart has been restored
- sudden blocking of an artery in the lungs (pulmonary embolism), 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)

- 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.
- 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)
- 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 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 (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

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.

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 – 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. Alteplase is produced by recombinant DNA technique using a Chinese hamster ovary cell-line. The other ingredients are arginine, phosphoric acid (for pH-adjustment) and polysorbate 80.
- The solvent is water for injections.

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 pack sizes:

- 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 pack sizes may be marketed.

Marketing Authorisation Holder
Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

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

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France

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The following information is intended for healthcare professionals only:

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.

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 mg, 20 mg 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 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:

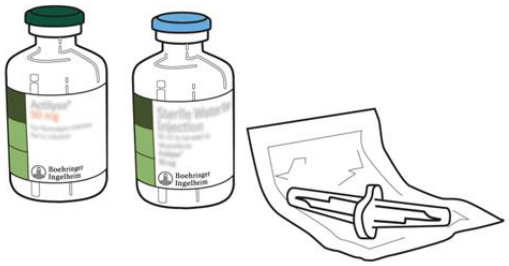
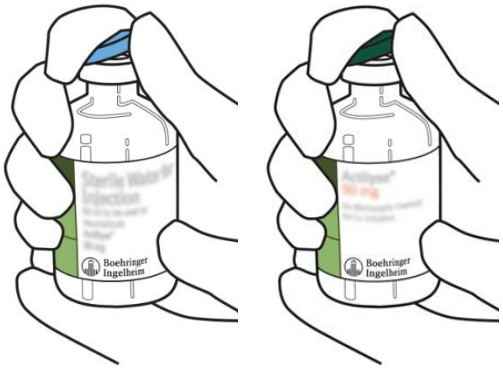
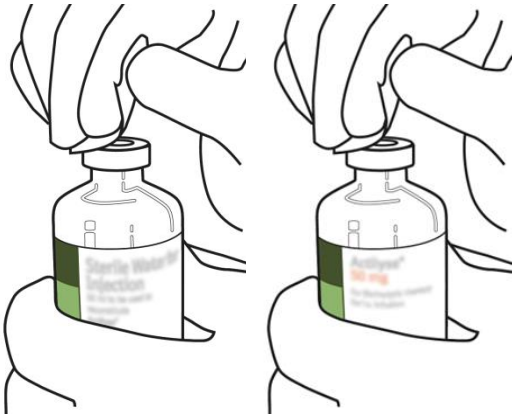
Actilyse dry substance	10 mg	20 mg	50 mg
a) Volume of sterilised water for injections to be added to dry substance	10 mL	20 mL	50 mL
Final concentration:	1 mg alteplase/mL	1 mg alteplase/mL	1 mg alteplase/mL
b) Volume of sterilised water for injections to be added to dry substance	5 mL	10 mL	25 mL
Final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

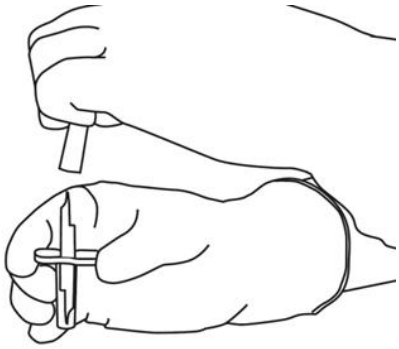
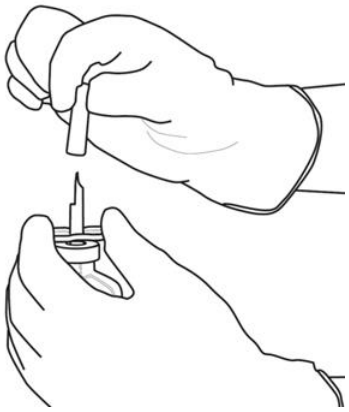
The reconstituted solution should then be administered intravenously. The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg/ml since the occurrence of turbidity of the reconstituted solution 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).

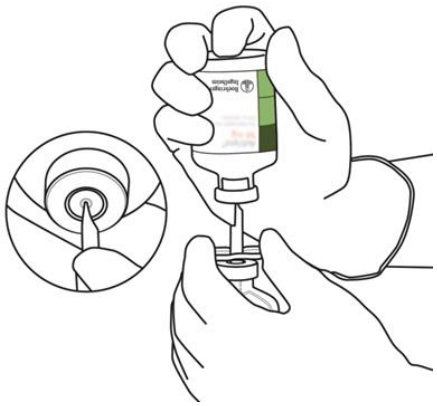
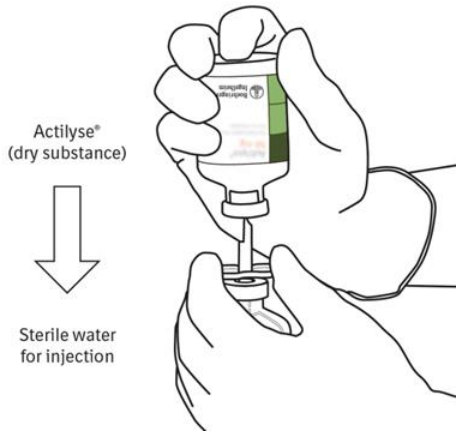
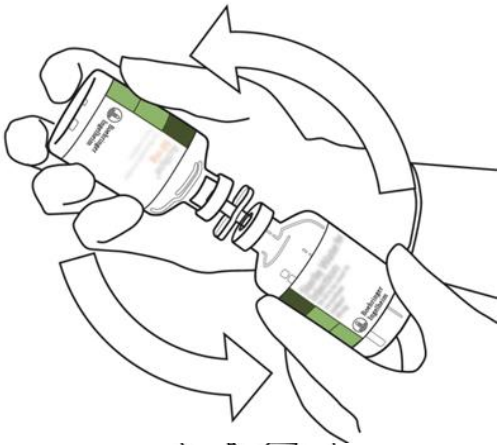
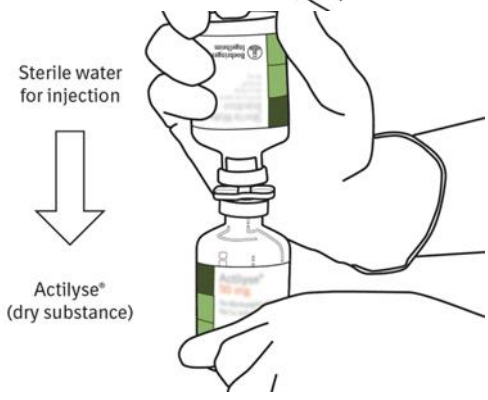
For storage conditions, please see section 5 of this leaflet.

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

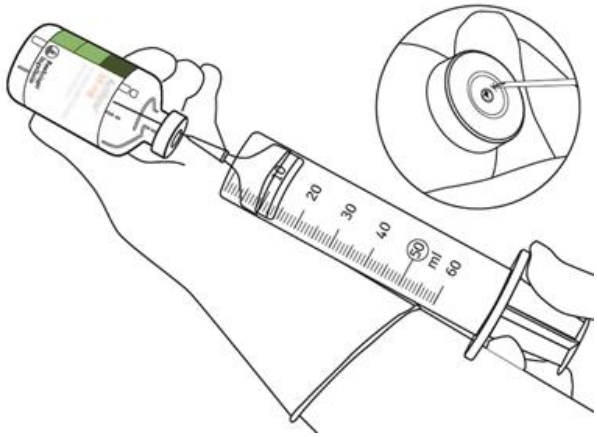
Instructions for reconstituting Actilyse

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 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 1 mg/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.)

Posology and method of administration

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	0.75 ml/ kg bw	0.375 ml/ kg bw

30 minutes, immediately followed by		
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.

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.

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.

Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms (see SmPC section 4.4). 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).

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 1 mg/mL over 60 min as a constant rate infusion.

Adjunctive therapy: 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 of onset of the symptoms 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.

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.