SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Actilyse
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 a 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.

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.

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 vial	10 mg	20 mg	50 mg
	Volume of water for injections to be added to dry powder:		
Final concentration (a) 1 mg alteplase/ml (ml)	10	20	50
(b) 2 mg alteplase/ml (ml)	5	10	25

The reconstituted solution should then be administered intravenously. It 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 dilution of the 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 neither in the same infusion-vial nor the same catheter (not even with heparin). For further practical instructions for preparation and handling see sections 6.2 and 6.6.

The experience in children and adolescents is limited. Actilyse is contraindicated for the treatment of acute stroke in children and adolescents (see section 4.3).

Myocardial infarction

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

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

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

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

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

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

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

The 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; acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued with lifelong treatment unless it is contraindicated.

Pulmonary embolism

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).

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.

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.

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 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 3 hours.

Additional contraindications in acute 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 3 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 or diastolic BP > 110 mm Hg, or aggressive management (intravenous pharmacotherapy) necessary to reduce BP to these limits
- blood glucose < 50 or > 400 mg/dl.

Use in children and, adolescents
Actilyse is not indicated for the treatment of acute stroke in paediatric patients under 18 years.

Use in elderly patients
Actilyse is not indicated for the treatment of acute stroke in adults over 80 years of age.

4.4 Special warnings and precautions for use

Special warnings and precautions in acute myocardial infarction, acute pulmonary embolism and acute ischaemic stroke:

Thrombolytic/fibrinolytic treatment requires adequate monitoring. Actilyse should only be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use. It is recommended that when Actilyse is administered standard resuscitation equipment and pharmacotherapy be available in all circumstances.

Hypersensitivity
No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systemic experience with re-administration of Actilyse. Anaphylactoid reactions associated with the administration of Actilyse are rare and can be caused by hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. The stopper of the glass vial with Actilyse power contains natural rubber (a derivative of latex) which may cause allergic reactions.

If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment initiated.

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

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

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).

Additional special warnings and precautions in acute myocardial infarction:

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

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

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

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

Additional special warnings and precautions in acute pulmonary embolism:

same as for acute myocardial infarction (see above)

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.

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
- with later time-to-treatment from onset of stroke symptoms the net clinical benefit is reduced and may be associated with a higher risk of ICH and death compared to patients treated earlier. 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..
-

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.

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

In patients with very mild stroke**,** the risks outweigh the expected benefit (see 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 over 80, patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 50 mg/dl or >400 mg/dl at baseline should not be treated with Actilyse (see section 4.3).

Data available from ECASS III and the pooled analysis indicate that the net clinical benefit becomes smaller in elderly with increasing age compared to younger patients as benefit from treatment with Actilyse appears to decrease and the risk of mortality appears to increase with increasing age.

Other special warnings:
Reperfusion of the ischaemic area may induce cerebral oedama 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 an anaphylactoid reaction, as in the cases describing such reactions a relatively larger proportion of patients were receiving ACE inhibitors concomitantly.
Concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

4.6 Pregnancy and lactation

There is very limited experience with the use of alteplase during pregnancy and lactation. Studies in animals have shown reproductive toxicity (see section 5.3). In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk. It is not known if alteplase is excreted into breast milk.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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 intracranial haemorrhage as adverse reaction in the indication stroke and 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.

<u>Haemorrhage</u>

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

very common:	bleeding from damaged blood vessels (such as haematoma) injection site haemorrhage (puncture site haemorrhage, catheter site haematoma, catheter site haemorrhage)
common:	intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage) in the treatment of acute ischaemic stroke. Symptomatic intracerebral haemorrhage represents the major adverse reaction in the treatment of acute ischaemic stroke (up to 10 % 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). respiratory tract haemorrhage (such as pharyngeal haemorrhage, epistaxis, haemoptysis) gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, haemorrhage rectum, haematemesis, melaena, mouth haemorrhage, gingival bleeding) ecchymosis urogenital haemorrhage (such as haematuria, haemorrhage urinary tract) blood transfusion (necessary)
uncommon:	intracranial 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 ear haemorrhage haemopericardium retroperitoneal haemorrhage (such as retroperitoneal haematoma)
rare:	bleeding in parenchymatous organs (such as hepatic haemorrhage, pulmonary haemorrhage)
very rare:	eye haemorrhage

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

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.

Immune system disorders

uncommom:	hypersensitivity reactions / anaphylactoid reactions (e.g. allergic reactions including rash, urticaria, bronchospasm, angio-oedema, hypotension, shock or any other symptom associated with allergic reactions)
very rare:	serious anaphylaxis

Transient antibody formation to Actilyse has been observed in rare cases and with low titres, but a clinical relevance of this finding could not be established.

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

As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and / or thrombolytic administration.

very common:	recurrent ischaemia / angina, hypotension and heart failure / pulmonary oedema, reperfusion arrhythmias (such as arrhythmia, extrasystoles, AV block I° to complete, atrial fibrillation / flutter, bradycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia / fibrillation, electromechanical dissociation [EMD])
common:	cardiac arrest, cardiogenic shock and reinfarction
uncommon:	mitral regurgitation, pulmonary embolism, other systemic embolism / cerebral embolism, ventricular septal defect

These cardiac events can be life-threatening and may lead to death.

Vascular disorders

uncommon:	embolism (thrombotic embolisation), which may lead to corresponding consequences in the organs concerned

Gastrointestinal disorders

common:	nausea, vomiting

Investigations

very common:	blood pressure decreased
common:	body temperature increased

Injury and poisoning and procedural complications

rare:	fat embolism (cholesterol crystal embolisation), which may lead to corresponding consequences in the organs concerned

4.9 Overdose

The relative fibrin specificity notwithstanding, a clinical significant reduction in fibrinogen and other blood coagulation components may occur after overdosage. In most cases, it is sufficient to await the physiological regeneration of these factors after the Actilyse therapy has been terminated. If, however, severe bleeding results, the infusion of fresh frozen plasma or fresh blood is recommended and if necessary, synthetic antifibrinolytics may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agent, ATC code: B 01 A D 02

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.

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.

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.

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.

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 stroke
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 symptomatic intracranial haemorrhage was higher with alteplase vs. placebo (27.0% vs 17.6%, p=0.0012; 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.

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 for solution:
Arginine
Phosphoric acid, dilute
Polysorbate 80

Solvent:
Water for injections

The pH of the reconstituted solution is 7.3 ± 0.5.

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

10 mg, 20 mg and 50 mg pack sizes: 3 years

After reconstitution, an immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C and for 8 hours at 25 °C.

6.4 Special precautions for storage

Store in the original package in order to protect from light.
For 10 mg, 20 mg and 50 mg pack sizes: Do not store above 25 °C.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution:
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 pack sizes, 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 pack sizes of 20 mg and 50 mg only)

Pack sizes:

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 pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For reconstitution to a final concentration of 1 mg altpelase per ml the full volume of solvent provided should be transfered 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 pack sizes 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. In these cases always a syringe should be used to transfer the required amount of solvent to the vial containing the Actilyse powder.

A table giving the volumes of solvent required for reconstitution to the final concentrations for each pack size is provided in section 4.2.

When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation.

The reconstituted preparation is a clear and colourless to pale yellow solution. Prior to administration it should be inspected visually for particles and colour.

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

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