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.

Ischaemic stroke: In two US studies (NINDS A/B) a significant higher proportion of patients with ischaemic stroke, when compared to placebo, had a favourable outcome (no or minimal disability). These findings were not confirmed in two European studies and an additional USA study. In the latter studies however, the majority of patients were not treated within 3 hours of stroke onset. In a meta-analysis of all patients treated within 3 hours after stroke onset the beneficial effect of alteplase was confirmed. The risk difference versus placebo for a good recovery was 14.9% (CI 95% 8.1% to 21.7%) despite an increased risk of severe and fatal intracranial haemorrhage. The data do not allow drawing a definite conclusion on the treatment effect on death. Nevertheless overall, the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the precautions stated, is considered favourable.

A meta-analysis of all clinical data show that, the agent is less effective in patients treated after 3 hours of onset (3 to 6 hours) compared with those treated within 3 hours of onset of symptoms, while the risks were higher, which makes the benefit/risk ratio of alteplase unfavourable outside the 0 - 3h time frame. 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.

Pharmacokinetics: ACTILYSE is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 ml/min.). The relevant plasma half-life T1/2 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 a half-life of about 40 minutes was measured.

**Indications**

1. Thrombolytic treatment in acute myocardial infarction.
   - 90 minutes (accelerated) dose regimen (see Dosage and administration): for patients in whom treatment can be started within 6 h of symptom onset;
   - 3 hour dose regimen (see Dosage and administration): for patients in whom treatment can be started between 6 - 12 h after symptom onset.
   - ACTILYSE has proven to reduce 30-day-mortality in patients with acute myocardial infarction.

2. Thrombolytic treatment in acute massive pulmonary embolism with haemodynamic instability. The diagnosis should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning. There are no clinical trials on mortality and late morbidity related to pulmonary embolism.

3. Thrombolytic treatment of acute ischaemic stroke. Treatment should only be initiated within 3 hours after the onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques such as cranial computed tomography (CT).

**Contraindications**

The following contraindications apply in general:

As with all thrombolytic agents, ACTILYSE should not be used 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 oral anticoagulants, e.g. warfarin sodium (INR >1.3)
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- history or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
- severe uncontrolled arterial hypertension
- major surgery or significant trauma in the past 10 days (this includes any trauma associated with the current acute myocardial infarction), recent trauma to head or cranium
- prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery, within the past 10 days, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- haemorrhagic retinopathy, e.g. in diabetes (vision disturbances may indicate haemorrhagic retinopathy) or other haemorrhagic ophthalmic conditions
- bacterial endocarditis, pericarditis
- acute pancreatitis
- documented ulcerative gastro-intestinal disease during the last 3 months
- arterial aneurysms, arterial/venous malformations
- neoplasm with increased bleeding risk
- hypersensitivity to the active substance alteplase or to any of the excipients

In the indications of acute myocardial infarction and pulmonary embolism the following contraindication applies in addition:

- History of stroke

In the indication acute ischaemic stroke the following contraindications apply in addition

- symptoms of ischaemic attack began more than 3 hours prior to infusion start or when time of symptom onset is unknown
- symptoms of acute ischaemic stroke that were either rapidly improving or only minor before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques
- seizure at the onset of stroke
- history of previous stroke or serious head-trauma within three months
- a combination of previous stroke and diabetes mellitus
- administration of heparin within 48 hours preceding the onset of stroke with an elevated activated partial thromboplastin time (aPTT) at presentation
- platelet count of less than 100,000 / mm3
- systolic blood pressure > 185 or diastolic blood pressure > 110 mm Hg, or aggressive management (IV medication) necessary to reduce blood pressure to these limits
- blood glucose <50 or > 400 mg/dl

ACTILYSE is not indicated for the therapy of acute stroke in children and adolescents under 18 years or adults over 80 years of age.

**Side effects**
The following adverse events, which may be causally related to the administration of ACTILYSE, have been reported. The most frequent adverse reaction associated with ACTILYSE is bleeding resulting in a fall in haematocrit and/or haemoglobin values. The type of bleeds associated with thrombolytic therapy can be divided into two broad categories:

- superficial bleeding, normally from punctures or damaged blood vessels,
- internal bleedings into the gastro-intestinal or urogenital tract, retro-peritoneum or CNS or bleeding of parenchymatous organs. Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes. The frequencies given below are based on corresponding occurrences in a clinical trial involving 8,299 patients treated with ACTILYSE for myocardial infarction.

The classification of cholesterol crystal embolisation, which was not observed in the clinical trial population, was based on spontaneous reporting. The number of patients treated in clinical trials in the indications pulmonary embolism and stroke (within the 0 - 3 hours time window) is very small in comparison to the number in the trial for myocardial infarction described above.

Therefore, small numerical differences observed in comparison with the number in myocardial infarction were presumably attributable to the small sample size. Except for intracranial haemorrhage as side effect 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 side effect profile of ACTILYSE in the indications pulmonary embolism and acute ischaemic stroke is different from the profile in the indication myocardial infarction.

**Indication myocardial infarction:**
Cardiac disorders: Very common: reperfusion arrhythmias, which can be life threatening and may require the use of conventional anti-arrhythmic therapies

**Indications myocardial infarction and pulmonary embolism:**
Nervous system disorders Uncommon: intracranial haemorrhage Indication acute ischaemic stroke:
Nervous system disorders: Common: intracranial haemorrhage. Symptomatic intracerebral haemorrhages represents the major adverse event (up to 10% of patients). However, this had not shown an increased overall morbidity or mortality.

**Indications myocardial infarction, pulmonary embolism and acute ischaemic stroke:**
Gastro-intestinal disorders: Common: bleeding into gastro-intestinal tract, nausea, vomiting. Nausea and vomiting can also occur as symptoms of myocardial infarction. Uncommon: bleeding into retro-peritoneum, gingival bleeding
General disorders and administration site conditions: Very common: superficial bleeding, normally from punctures or damaged blood vessels
As fibrin is lysed during ACTILYSE therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including those following catheter insertion, arterial and venous puncture cutdown and needle puncture). The use of rigid catheters, intramuscular injections and non-essential handling of the patient should be avoided during treatment with ACTILYSE.

Should serious bleeding occur, in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued and concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents should also be considered. A dose exceeding 100 mg of ACTILYSE should not be given in acute myocardial infarction as well as pulmonary embolism and 90 mg in acute ischaemic stroke because it has been associated with an increase in intracranial bleeding.

As yet, there is only limited experience with the use of ACTILYSE in children.

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. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment should be initiated. Monitoring is recommended particularly for patients receiving ACE-inhibitors concomitantly (see Side effects). As with all thrombolytics, the use of ACTILYSE therapy has to be carefully evaluated in order to balance the potential risks of bleeding with expected benefits under the following conditions:

**Special warnings and precautions**

ACTILYSE should be used by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor that use. As with other thrombolytics, it is recommended that when ACTILYSE is administered standard resuscitation equipment and medication be available in all circumstances.

**The following special precautions apply in general:**

- **Bleeding:** The most common complication encountered during ACTILYSE therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding.
patients pre-treated with acetyl salicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if ACTILYSE treatment is delayed. Not more than 0.9 mg alteplase/kg bodyweight (max. of 90 mg) should be administered in view of the increased risk of cerebral haemorrhage. Treatment should not be initiated later than 3 hours after the onset of symptoms because of unfavourable benefit/risk ratio mainly based on the following:
- positive treatment effects decrease over time
- particularly in patients with prior ASA treatment the mortality rate increases
- increased risk of symptomatic haemorrhage.

Blood pressure (BP) monitoring during treatment administration and up to 24 hours is necessary; i.v. antihypertensive therapy is recommended if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg. The therapeutic benefit is reduced in patients who have had a prior stroke or in whom uncontrolled diabetes exists. The benefit/risk ratio is considered less favourable, although still positive in these patients.

In patients with very mild stroke, the risks outweigh the expected benefit and they should not be treated with ACTILYSE.

Patients with very severe stroke are at higher risk of intracerebral haemorrhage and death and should not be treated with ACTILYSE.

Patients with extensive infarctions are at greater risk of poor outcome including severe haemorrhage and death. In such patients, the benefit/risk ratio should be thoroughly considered.

In stroke patients the likelihood of a favourable outcome decreases with increasing age, increasing stroke severity and increased levels of blood glucose on admission while the likelihood of severe disability and death or relevant intracranial bleeding increases, independently of 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.

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.

**Drug Interactions**
No formal interaction studies with ACTILYSE and medicinal products commonly administered in patients with acute myocardial infarction have been performed. Medicinal products that affect coagulation or those that alter platelet function may increase the risk of bleeding prior to, during or after ACTILYSE therapy. 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.

**Incompatibilities**
The reconstituted solution may be diluted further with sterile physiological saline function (0.9%) up to a minimal concentration of 0.2 mg alteplase per ml. It may not, however, be diluted further with water for injections or carbohydrate infusion solutions, e.g. dextrose. ACTILYSE must not be mixed with other drugs, neither in the same infusion-vial nor via the same venous line (not even with heparin).

**Pregnancy and lactation**
There is very limited experience with the use of ACTILYSE during pregnancy and lactation. 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.

**Dosage and administration**
ACTILYSE should be given as soon as possible after symptom onset.

1. **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:

   - 15 mg as an intravenous bolus, 50 mg as an infusion over the first 30 minutes, followed by an infusion of 35 mg over 60 minutes, until the maximal dose of 100 mg.

   b) 3 h dose regimen for patients, in whom treatment can be started between 6 and 12 hours after symptom onset: 10 mg as an intravenous bolus, 50 mg as an intravenous infusion over the first hour, followed by infusions of 10 mg over 30 minutes, until the maximal dose of 100 mg over 3 hours.

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

   The accepted maximum dose in acute myocardial infarction is 100 mg alteplase.

   **Adjunctive therapy:**

   Acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued for the first months after myocardial infarction. The recommended dose is 160 - 300 mg/d. Heparin should be administered concomitantly for 24 hours or longer (at least 48 hours with the accelerated dose regimen). It is recommended to start with an initial intravenous bolus of 5,000 units prior to thrombolytic therapy and to continue with an infusion of 1,000 units/hour. The dose of heparin should be adjusted according to repeated measurements of aPTT values of 1.5 to 2.5 folds of the initial value.

2. **Pulmonary embolism**

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

   - 10 mg as an intravenous bolus over 1-2 minutes,
   - 90 mg as an intravenous infusion over two hours.

   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 according to aPTT values of 1.5 to 2.5 fold of the initial value.
3. Ischaemic stroke
The recommended dose is 0.9 mg/kg (maximum of 90 mg) infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus. Therapy should be initiated as early as possible within 3 hours after onset of symptoms.

Adjunctive therapy:
The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid during the first 24 hours after the symptom-onset has not been investigated sufficiently. Therefore, 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.

Instructions for use/handling
Under aseptic conditions the contents of an injection vial of ACTILYSE (50 mg) dry substance is dissolved with water for injection according to the following table to obtain a final concentration of 1 mg alteplase per ml.

<table>
<thead>
<tr>
<th>ACTILYSE® vial</th>
<th>Volume of water for injections to be added to dry substance</th>
</tr>
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<tbody>
<tr>
<td>50 mg</td>
<td>50 ml</td>
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</table>

Thus, for reconstitution to the final concentration of 1 mg alteplase/ml the full volume of solvent provided should be transferred to the vial containing the ACTILYSE dry substance. For this purpose a transfer cannula is included with the pack-size of 50 mg.

The reconstituted solution should then be administered intravenously as described above. The reconstituted solution may be diluted further with sterile physiological saline solution (0.9%) up to a minimal concentration of 0.2 mg alteplase per ml. It may not, however, be diluted with water for injections or carbohydrate infusion solutions, e.g. dextrose. ACTILYSE must not be mixed with other drugs, neither in the same infusion-vial nor via the same venous line (not even with heparin).

Overdose
The relative fibrin specificity notwithstanding, a clinical significant reduction in fibrinogen and other blood coagulation components may occur after overdose. 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.

Special precautions for storage
Protect the lyophilised substance from light. Store below 30°C

Reconstituted solution
The prepared solution may be stored in a refrigerator up to 24 hours and up to 8 hours at temperatures not exceeding 30°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.

Availability
Pack with 1 vial containing 50 mg of the active ingredient and 1 vial with 50 ml water for injections (Packed as a Treatment-set containing 2 packs ACTILYSE 50 mg with 50 ml water for injections and i.v. kit)