AUSTRALIAN PRODUCT INFORMATION – ACTILYSE (alteplase) powder for injection

1 NAME OF THE MEDICINE

alteplase (rch)

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION and PHARMACEUTICAL FORM

ACTILYSE is presented as a sterile, white to off-white, lyophilised powder, intended for intravenous administration after reconstitution with sterilised Water for Injections.

ACTILYSE 10 mg

Box containing 1 vial of ACTILYSE 10 mg alteplase (corresponding to 5,800,000 IU) in up to 466.6 mg dry powder, 1 vial of sterilised Water for Injections, 10 mL.

ACTILYSE 20 mg*

Box containing 1 vial of ACTILYSE 20 mg alteplase (corresponding to 11,600,000 IU) in 933.2 mg dry powder, 1 vial of sterilised Water for Injections, 20 mL, and 1 transfer cannula for preparing a sterile solution of ACTILYSE.

ACTILYSE 50 mg

Box containing 1 vial of ACTILYSE 50 mg alteplase (corresponding to 29,000,000 IU) in 2333 mg dry powder, 1 vial of sterilised Water for Injections, 50 mL, and 1 transfer cannula for preparing a sterile solution of ACTILYSE.

*Not currently distributed in Australia.

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 List of excipients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Myocardial Infarction

ACTILYSE is indicated for intravenous use in adults for the lysis of suspected occlusive coronary artery thrombi associated with evolving transmural myocardial infarction. Treatment should be initiated as soon as possible after the onset of symptoms. The treatment can be initiated within 12 hours of symptom onset.

Pulmonary Embolism

ACTILYSE is also indicated in patients with acute massive pulmonary embolism in whom thrombolytic therapy is considered appropriate.

Acute Ischaemic Stroke

ACTILYSE is indicated for thrombolytic 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 DOSE AND METHOD OF ADMINISTRATION

Administer ACTILYSE as early as possible after onset of symptoms. ACTILYSE is intended for intravenous use only. It should be given via a dedicated intravenous line with an infusion pump.

A total dose *exceeding 100 mg* of ACTILYSE should not be used for the treatment of acute myocardial infarction or acute massive pulmonary embolism because it has been associated with an increase in intracranial bleeding. For the same reason, the total dose used for the treatment of acute ischaemic stroke should not exceed *90 mg*.

Acute Myocardial Infarction

a) Accelerated Infusion

The accelerated dosage regimen is based on the results from the GUSTO Study (See Section 5.1 Pharmacodynamic Properties – Clinical trials).

For patients weighing ≥65 kg, the recommended total dose is 100 mg administered as follows:

- 15 mg intravenous bolus, immediately followed by
- 50 mg intravenous infusion over the first 30 minutes, immediately followed by an intravenous infusion of
- 35 mg over the following 60 minutes.

For patients weighing <65 kg, the dose is adjusted on the basis of bodyweight as follows:

- 15 mg intravenous bolus, immediately followed by
- 0.75 mg/kg as an intravenous infusion over the first 30 minutes (maximum 50 mg), immediately followed by an intravenous infusion of
- 0.5 mg/kg over the following 60 minutes (up to a maximum of 35 mg).

b) 3 Hour Infusion

For a description of the trials this dosage regimen is based on, see Section 5.1 Pharmacodynamic Properties – Clinical trials.

For patients weighing ≥65 kg, the recommended total dose is 100 mg administered as follows:

- 10 mg intravenous bolus, immediately followed by
- 50 mg intravenous infusion over the first hour, immediately followed by an intravenous infusion of
- 40 mg over the following 2 hours.

For patients weighing <65 kg, the dose is adjusted on the basis of bodyweight as follows:

- 10 mg as an intravenous bolus, immediately followed by
- an intravenous infusion up to a maximum total dose of 1.5 mg/kg body weight over three hours.

Adjunctive Therapy:

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

For the antithrombotic adjunctive therapy regimen used in the GUSTO study, see Section 5.1 Pharmacodynamic Properties – Clinical trials.

Acute massive pulmonary embolism

For patients weighing ≥ 65 kg, a total dose of 100 mg should be administered over 2 hours. The most experience available is with the following dose regimen:

- 10 mg as an intravenous bolus over 1-2 minutes, immediately followed by
- 90 mg as an intravenous infusion over two hours until the total dose of 100 mg.

In patients with a bodyweight below 65 kg:

- 10 mg as an intravenous bolus over 1 – 2 minutes, immediately followed by
- an intravenous infusion up to a maximum total dose of 1.5 mg/kg body weight over two hours.

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 1.5 to 2.5 fold of the reference value (50-70 seconds).

Acute Ischaemic Stroke

Treatment must be performed by a physician specialised in neurological care. (See Section 4.4 Special Warnings and Precautions for Use – Additional Warnings in Acute Ischaemic Stroke)

The recommended total dose is 0.9 mg alteplase/kg bodyweight (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.

Treatment with ACTILYSE should be initiated as early as possible within 4.5 hours of symptom onset, see Section 4.4 Special Warnings and Precautions for Use – Additional Warnings in Acute Ischaemic Stroke. The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

DOSING TABLE FOR ACUTE ISCHAEMIC STROKE

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.

Adjunctive therapy:

The safety and efficacy of this regimen with concomitant administration of heparin, oral anticoagulants or platelet aggregation inhibitors such as aspirin within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of intravenous heparin or platelet aggregation inhibitors such as aspirin 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.

Instructions for use

Do not use vial if vacuum is not present.

Under aseptic conditions the contents of an injection vial of ACTILYSE (10 mg, 20 mg or 50 mg) dry substance is dissolved with sterilised water for injection according to the following table to obtain a final concentration of 1 mg alteplase per mL.

ACTILYSE dry substance	10 mg	20 mg	50 mg
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

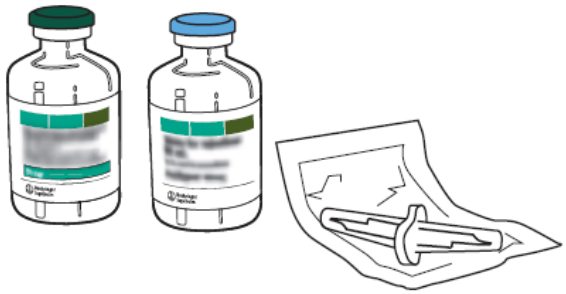
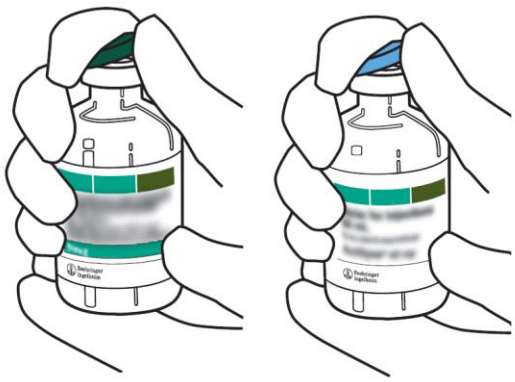
For this purpose a transfer cannula is included with the pack sizes of 20 mg and 50 mg. For the pack size 10 mg a syringe should be used.

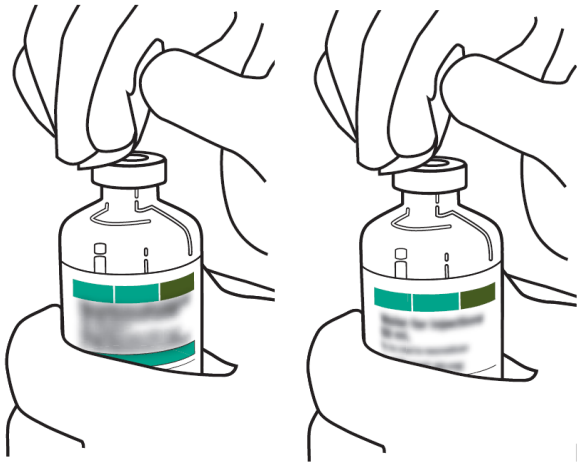
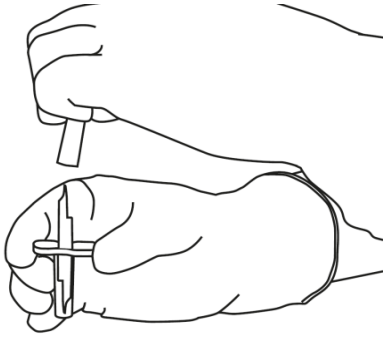
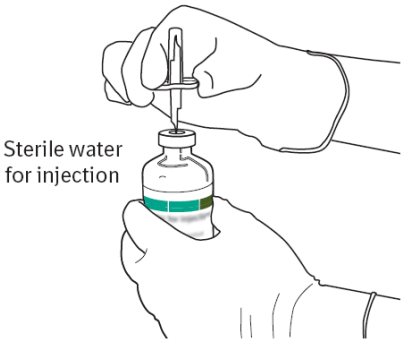
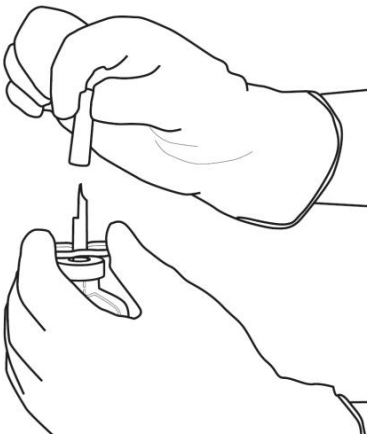
It is important that ACTILYSE be reconstituted only with sterilised Water for Injections without preservatives. Do not use bacteriostatic Water for Injections.

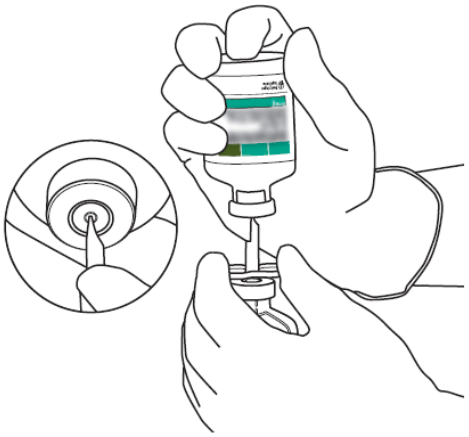
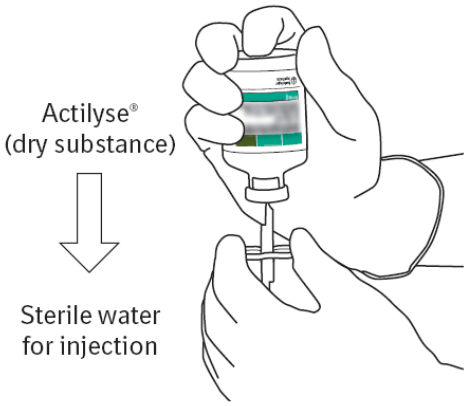
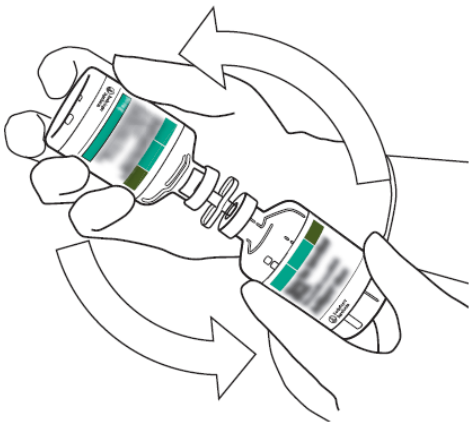
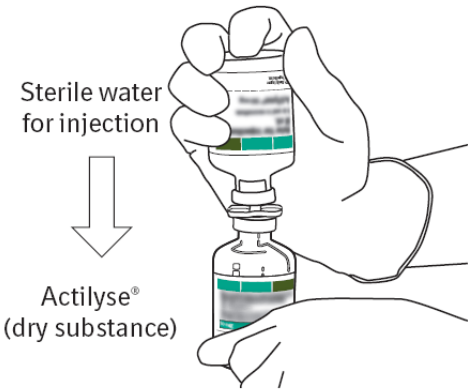
The reconstituted lyophilised preparation results in a colourless to pale yellow transparent solution containing ACTILYSE 1.0 mg/mL at a pH of 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

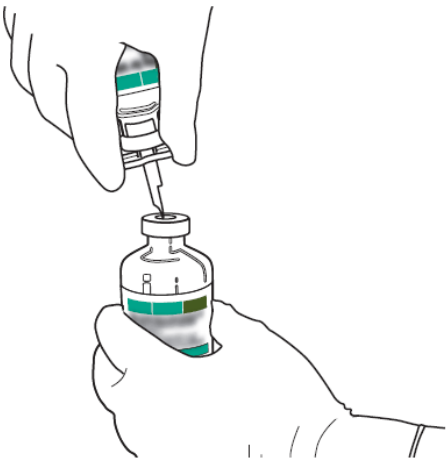
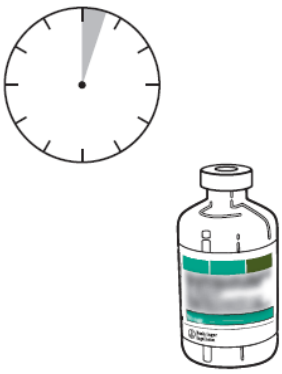
ACTILYSE should not be mixed with other drugs, neither in the same infusion vial nor the same venous line (not even with heparin). Before dilution or administration, parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration whenever solution and container permit.

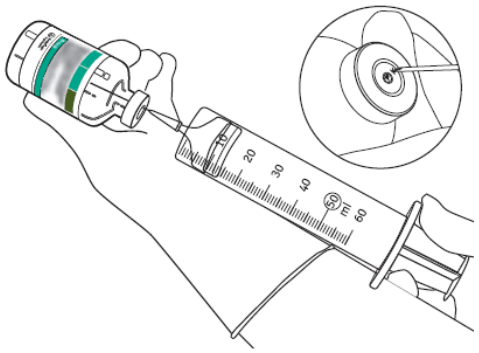
Instructions for reconstituting ACTILYSE

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 sterilise 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 centre with the transfer cannula, by pressing gently but firmly, without twisting. Note: pressing with excessive force may push the rubber stopper into the vial.	
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 centre 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 ACTILYSE. 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. Note: pushing a giving set or other inappropriate device into the stopper may push the rubber stopper into the vial.	
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.)

Dilution

The reconstituted solution (1 mg alteplase per mL) may be diluted further, immediately before administration, with sterilised physiological saline solution (0.9% Sodium Chloride for Injection) up to a minimal concentration of 0.2 mg alteplase per mL. Further dilution of the reconstituted solution with sterile physiological saline solution (0.9% Sodium Chloride for Injection) below a minimal concentration of 0.2 mg alteplase per mL is not recommended 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, carbohydrate infusion solutions (e.g. glucose), or preservative containing solutions is not recommended due to increasing formation of turbidity of the reconstituted solution.

Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion.

No other medication should be added to ACTILYSE solution. Because ACTILYSE contains no preservatives, it should be reconstituted immediately before use.

4.3 CONTRAINDICATIONS

ACTILYSE is contraindicated in patients with known hypersensitivity to the active substance alteplase or any of the excipients (listed under Section 6.1 List of Excipients).

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
- History or evidence of or suspected intracranial haemorrhage, including subarachnoid haemorrhage
- History of central nervous system damage (e.g. neoplasm, aneurysm, intracranial or spinal surgery)
- Severe uncontrolled hypertension
- Recent (within 10 days) prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery, organ biopsy, puncture of noncompressible blood vessel (e.g. subclavian or jugular vein puncture)
- Major surgery (e.g. coronary artery bypass graft) or significant trauma (including any trauma associated with acute myocardial infarction) within the past 3 months, recent trauma to the head or cranium
- Documented ulcerative gastrointestinal disease during the last 3 months
- Arterial aneurysms, arterial/venous malformations
- Neoplasm with increased bleeding risk
- Bacterial endocarditis, pericarditis

- Acute pancreatitis
- Haemostatic defects including those secondary to severe hepatic or renal disease; special attention should be paid to coagulation parameters in patients with significant liver dysfunction
- Severe hepatic disease/dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
- Patients receiving other intravenous thrombolytic agents
- Patients currently receiving effective oral anticoagulant treatment (e.g. warfarin sodium with INR> 1.3), see Section 4.4 Special Warnings and Precautions for Use, Bleeding

Additional Contraindications for Patients with Acute Myocardial Infarction / Acute Massive Pulmonary Embolism:

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months, except current acute ischaemic stroke within 4.5 hours

Additional Contraindications for Patients with Acute Ischaemic Stroke:

- Symptoms of ischaemic attack began more than 4.5 hours prior to infusion start or when time of symptom onset is unknown
- 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 due to a higher risk of intracerebral haemorrhage and death
- 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 48 hours preceding the onset of stroke and with an elevated activated partial thromboplastin time (aPTT) at presentation
- History of prior stroke and concomitant diabetes
- History of previous stroke or serious head-trauma within the last 3 months
- Platelet count of below 100,000/mm^3
- Systolic blood pressure (BP) > 185 mm Hg or diastolic BP > 110 mm Hg, or aggressive management (IV medication) necessary to reduce BP to these limits
- Blood glucose < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L)
- Patients < 18 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Traceability

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

Bleeding

The most common complication encountered during therapy with ACTILYSE is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding at any site or body cavity;
- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g. venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of other active substances affecting coagulation or platelet function (e.g. heparin anticoagulation) undoubtedly contributes to the bleeding.

Fibrin will be lysed during the infusion of ACTILYSE and bleeding from recent puncture sites may occur. Therefore, therapy with ACTILYSE, as with other thrombolytic agents, requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

The use of rigid catheters, intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTILYSE. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTILYSE, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, in particular cerebral haemorrhage, the infusion of ACTILYSE and any concomitant heparin should be terminated immediately and treatment instituted as described under Section 4.9 Overdose.

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:

- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions (vision disturbances may indicate haemorrhagic retinopathy);
- Recent minor traumas (within 10 days), such as biopsies, puncture of major vessels, intramuscular injections, cardiopulmonary resuscitation;
- Any other conditions not mentioned under Section 4.3 Contraindications in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location;
- Patients receiving oral anticoagulants treatment: The use of ACTILYSE may be considered when appropriate test(s) of anticoagulant activity for the product(s) concerned show no clinically relevant activity.

Cholesterol Embolisation

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g. cardiac catherisation, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Additional Warnings in Acute Myocardial Infarction / Acute Massive Pulmonary Embolism

Additionally, the potential risks of ACTILYSE therapy should be carefully evaluated against the expected benefits in patients treated for acute Myocardial Infarction / acute massive Pulmonary Embolism with the following conditions:

- Systolic blood pressure > 160 mm Hg
- Advanced age, which may increase the risk of intracerebral haemorrhage. As there is also a therapeutic benefit to these patients, the risk-benefit evaluation should be carried out carefully.
- The use of thrombolytics can increase the risk of thrombo-embolic events in patients with left heart thrombus, e.g. mitral stenosis or atrial fibrillation
- Clinical evidence or history of ischaemic stroke or transient ischaemic attacks more than 6 months previously (see Section 4.3 Contraindications)

- A history or clinical evidence of hypertensive disease in a patient over 70 years old
- Septic thrombophlebitis or occluded AV cannula at seriously infected site.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarisations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction. Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTILYSE are administered.

Use of Anticoagulants

In the management of acute myocardial infarction or acute massive pulmonary embolism, antithrombotic adjunctive therapy such as heparin may be administered concomitantly with and following infusion of ACTILYSE to reduce the possibility of reocclusion (see Section 4.2 Dose and Method of Administration). The usual doses of heparin used may increase the risk of bleeding, independent of ACTILYSE. Because either heparin or ACTILYSE alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

The concomitant use of GP IIb/IIIa receptor antagonists increases the risk of bleeding.

Additional Warnings in Acute Ischaemic Stroke:

Treatment must be performed under the responsibility of a physician trained and experienced in neurological care. For the verification of treatment indication, remote diagnostic measures may be considered as appropriate (see Section 4.1 Therapeutic Indications, Acute Ischaemic Stroke).

Before ACTILYSE treatment is initiated, timely imaging evidence must be obtained to exclude intracranial haemorrhage, e.g. by cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage.

<u>Bleeding</u>

Intracerebral haemorrhages represents the major adverse events (up to approximately 15% of patients). However, this had not shown an increased overall morbidity or mortality.

Compared to other indications, patients with acute ischaemic stroke treated with ACTILYSE have a significantly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:

- Any situations involving a high risk of haemorrhage (see Section 4.3 Contraindications)
- Late time-to-treatment onset
- Patients pre-treated with aspirin may have a greater risk of intracerebral haemorrhage, particularly if ACTILYSE treatment is delayed.
- Due to an increased haemorrhagic risk, treatment with platelet aggregation inhibitors should not be initiated within the first 24 hours following thrombolysis with ACTILYSE (see Section 4.2 Dose and Method of Administration).
- Compared to younger patients, patients of advanced age (over 80 years) may have a somewhat poorer outcome independent of treatment. They may also have more severe strokes which are associated with a higher absolute risk of intracerebral haemorrhage when thrombolysed compared 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, the benefit-risk of thrombolysis in patients of advanced age remains positive. Thrombolysis in acute ischaemic stroke patients of any age should be evaluated on an individual benefit-risk basis. Patients of advanced age should be selected very carefully taking into account both the general health and the neurological status.

ACTILYSE treatment must not be initiated later than 4.5 hours after the onset of stroke symptoms (see Section 4.3 Contraindications) because of an unfavourable benefit/risk ratio mainly based on the following:

- Positive treatment effects decrease over time
- Particularly in patients with prior aspirin treatment the mortality rate increases
- Risk increases with regard to symptomatic haemorrhages

Blood pressure monitoring

Blood pressure (BP) monitoring during treatment administration and up to 24 hours is necessary. Intravenous antihypertensive therapy is recommended if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg.

Special patient groups at reduced benefit-risk

The therapeutic benefit is reduced in patients who had a prior stroke. Thus the benefit/risk ratio is considered less favourable, but still positive in these patients.

The therapeutic benefit is reduced in patients in whom uncontrolled diabetes is known. Thus the benefit/risk ratio is considered less favourable, but still positive in these patients.

For patients with both conditions (with a history of prior stroke and concomitant diabetes) the use of ACTILYSE is contraindicated (see Section 4.3 Contraindications).

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 longer time to treatment from onset of symptoms, increasing age, increasing stroke severity and increased levels of blood glucose on admission; while the likelihood of severe disability and death or symptomatic intracranial bleeding increases, independently from treatment. The use of ACTILYSE in patients over 80 years of age should be weighed carefully against anticipated risks on an individual basis (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Cerebral oedema

Reperfusion of ischaemic area may induce cerebral oedema in the infarcted zone.

General

ACTILYSE should be administered in a setting where the appropriate diagnostic and monitoring techniques are readily available.

Routine management of myocardial infarction should not be deferred after evidence of successful thrombolysis is seen. Evaluation for presence of underlying artherosclerotic heart disease should be carried out as clinically indicated.

The diagnosis of acute massive pulmonary embolism should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning.

It should be realised that the treatment of acute massive pulmonary embolism with ACTILYSE has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of re-embolisation due to the lysis of underlying deep venous thrombi should be considered.

Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimised. In the event of serious bleeding, ACTILYSE and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Current data generally do not support the use of thrombolytic therapy in patients when the ECG shows only ST depression (with the exception of those patients with a “true posterior” infarct, as indicated by tall R waves and marked ST depression in leads V_1 - V_3).

Hypersensitivity

Immune-mediated hypersensitivity reactions associated with the administration of ACTILYSE can be caused by the active substance alteplase or any of the excipients (see also Section 4.3 Contraindications).

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 Interactions with Other Medicines and Other Forms of Interactions). Patients treated for any authorised indication should be monitored for angio-oedema during and for up to 24 hours 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.

Use in the Elderly

The risks of therapy may be increased in the elderly. In a pooled analysis of randomised controlled clinical trials, patients over 80 years was associated with an increased risk of haemorrhage (both ICH and symptomatic ICH), mortality and decreased efficacy compared to younger patients (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Paediatric use

Safety and effectiveness of ACTILYSE in children has not been established. Therefore treatment of such patients is not recommended. ACTILYSE is not indicated for treatment of acute stroke in patients less than 18 years of age.

Effects on Laboratory Tests

During ACTILYSE infusion, coagulation tests and/or measures of fibrinolytic activity may be performed if desired. However, routine measurements of fibrinogen as well as fibrinogen degradation products are unreliable, and should not be undertaken unless specific precautions are taken to prevent *in vitro* artifacts. ACTILYSE is a serine protease that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions.

This can lead to degradation of fibrinogen in a blood sample removed for analysis. Collection of blood samples on aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs affecting coagulation/platelet function

The risk of haemorrhage may be increased with the use of coumarin derivatives, direct oral anticoagulants, antiplatelet aggregation agents, heparin or any other agent which influences haemostasis (before, during or within the first 24 hours after treatment with ACTILYSE). Treatment with these products should be avoided in the first 24 hours after treatment for acute ischaemic stroke (see Section 4.2 Dosage and Method of Administration).

The concomitant use of GP IIb/IIIa antagonists increases the risk of bleeding.

ACE inhibitors

Concomitant treatment with ACE inhibitors may enhance the risk of suffering an anaphylactoid reaction (see Section 4.8 Adverse Effects (Undesirable Effects)).

Other medicines

The interaction of ACTILYSE with other drugs has not been studied. Data on adjunctive pharmacotherapy during thrombolysis with ACTILYSE (e.g. calcium channel blockers, beta adrenergic blockers, etc.) are inadequate to exclude any possible drug interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies with ACTILYSE have not been performed to determine effect on fertility or reproduction.

Use in Pregnancy (Category B1)

Studies have shown that ACTILYSE is not teratogenic in the rat and rabbit and does not cross the placental barrier in the pregnant rat. In the rabbit, however, a dose-related increase in abortions and resorption rate was seen in the dose range 3-10 mg/kg/day. ACTILYSE should be given to pregnant women only if the need clearly outweighs the potential risk.

Use in Lactation

It is not known whether ACTILYSE is excreted in human milk. Because many drugs are excreted by this route, caution should be exercised when ACTILYSE is administered to a nursing woman and a decision must be made whether breast-feeding should be discontinued for the first 24 hours after administration of ACTILYSE.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

Summary of the safety profile

The most frequent adverse reaction associated with ACTILYSE is bleeding (≥1/100 to <1/10 major bleeds; ≥1/10 any haemorrhage) which may result in a fall in haematocrit and/or haemoglobin values. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanent disability or death.

Neurological symptoms such as somnolence, aphasia, hemiparesis, convulsion, epileptic seizure, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression and psychosis may be associated with intracranial haemorrhage.

The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding at any site or body cavity;
- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g. venous cutdowns, arterial punctures, sites of recent surgical intervention).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTILYSE therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Death and permanent disability are not uncommonly reported in patients that have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

The overall in-hospital mortality in myocardial infarction patients from all causes receiving ACTILYSE averaged 5-6%.

The following adverse reactions have been reported among patients receiving ACTILYSE in clinical trials and in post-marketing experience. The frequencies given below are based on adverse events reported for one or all three indications which may be causally related to ACTILYSE treatment.

The number of patients treated in clinical trials in the indications acute massive pulmonary embolism and acute ischaemic stroke (within the 0 - 4.5 hours time window) was smaller than the number in trials for acute myocardial infarction (see Section 5.1 Pharmacodynamic Properties – Clinical trials). Except for intracranial haemorrhage as a side effect in the acute ischaemic stroke indication and reperfusion arrhythmias in the acute myocardial infarction indication, there is no medical reason to

assume that the qualitative/quantitative side effect profile of ACTILYSE would differ between the three indications.

a) Adverse events related specifically to one or more indications

Cardiac disorders (related to acute myocardial infarction indication only):

≥1/10: reperfusion arrhythmias, such as

- arrhythmia
- extrasystoles
- atrial fibrillation
- first degree atrioventricular block to complete atrioventricular block
- bradycardia
- tachycardia
- ventricular arrhythmia
- ventricular fibrillation
- ventricular tachycardia occur in close temporal relationship to treatment with ACTILYSE

Nervous system disorders (related to acute ischaemic stroke indication only):

≥1/10: intracranial haemorrhage, such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation of stroke
- intracranial haematoma
- subarachnoid haemorrhage

Nervous system disorders (related to acute myocardial infarction and acute massive pulmonary embolism indications):

≥1/100 and <1/10: intracranial haemorrhage, such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation of stroke
- intracranial haematoma
- subarachnoid haemorrhage

b) Adverse events related to all three indications

General disorders and administration site conditions:

≥1/10: injection site haemorrhage, puncture site haemorrhage, such as

- catheter site haematoma
- catheter site haemorrhage

Investigations:

≥1/10: blood pressure decreased

≥1/100 and <1/10: body temperature increased

Vascular disorders:

≥1/10: haemorrhage (such as haematoma)

≥1/1,000 and <1/100: embolism, which may lead to corresponding consequences in the organs concerned

≥1/10,000 and <1/1,000: bleeding of parenchymatous organs, such as hepatic haemorrhage

Renal and urinary disorders:

≥1/100 and <1/10: urogenital haemorrhage, such as

– haematuria
– haemorrhage urinary tract

Respiratory, thoracic and mediastinal disorders:

≥1/100 and <1/10: respiratory tract haemorrhage, such as
– pharyngeal haemorrhage
– haemoptysis
– epistaxis

≥1/1,000 and <1/100: pulmonary haemorrhage

Surgical and medical procedures:

≥1/100 and <1/10: transfusion

Skin and subcutaneous tissue disorders:

≥1/100 and <1/10: ecchymosis

Gastrointestinal disorders:

≥1/100 and <1/10: gastrointestinal haemorrhage, such as
– gastric haemorrhage
– gastric ulcer haemorrhage
– rectal haemorrhage
– haematemesis
– melaena
– mouth haemorrhage
– nausea
– vomiting
– gingival bleeding

Nausea and vomiting can also occur as symptoms of myocardial infarction.

≥1/1,000 and <1/100: retroperitoneal haemorrhage, such as
– retroperitoneal haematoma

Immune system disorders:

≥1/1,000 and <1/100: anaphylactoid reactions, which are usually mild, but can be life threatening in isolated cases

They may appear as
– rash
– urticaria
– bronchospasm
– angio-oedema
– hypotension
– shock or any other symptom associated with hypersensitivity

Cardiac disorders:

≥1/1,000 and <1/100: pericardial haemorrhage

Injury and poisoning and procedural complications

≥1/10,000 and <1/1,000: fat embolism, which may lead to corresponding consequences in the organs concerned

Fat embolism was not observed in the clinical trial population, but was found in spontaneous reporting.

Eye disorders:

≥1/10,000 and <1/1,000: eye haemorrhage

As with other thrombolytic agents, the following events have been reported as sequelae of the underlying disease and/or thrombolytic administration and the effect of ACTILYSE on the incidence of these events is unknown. These events may be life threatening and may lead to death.

Use in acute myocardial infarction:

- recurrent ischemia / angina
- heart failure
- cardiogenic shock
- myocardial re-infarction
- myocardial rupture
- electromechanical dissociation
- pericardial effusion
- pericarditis
- mitral regurgitation
- cardiac tamponade
- pulmonary oedema
- ventricular septal defect

Use in acute massive pulmonary embolism:

- pulmonary re-embolisation
- pulmonary oedema
- pleural effusion
- hypotension

Use in acute ischemic stroke:

- cerebral oedema
- cerebral herniation
- seizure
- new ischemic stroke

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

Symptoms

If the maximum recommended dose is exceeded the risk of intracranial bleeding increases.

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

Therapy

Should serious bleeding occur in a critical location, in particular cerebral haemorrhage, the infusion of ACTILYSE and any other concomitant anticoagulant therapy should be discontinued immediately. Most patients can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement and manual pressure applied to the bleeding vessel if accessible. Protamine should be considered if heparin has been administered within 4 hours of the onset of bleeding. If necessary, blood loss and reversal of the bleeding tendency can be managed with fresh whole blood or packed red blood cells. In the event of clinically significant fibrinogen depletion, fresh frozen plasma or cryoprecipitate can be infused with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents may be used as a last option.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antithrombotic agents, ATC code: B01AD02

Mechanism of action

ACTILYSE is a serine protease which has the property of fibrin-enhanced conversion of plasminogen to plasmin. ACTILYSE produces minimal conversion of plasminogen in the absence of fibrin; and when introduced into the systemic circulation, ACTILYSE binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with minimal systemic effects.

ACTILYSE at a dose of 100 mg leads to a modest decrease of the circulating fibrinogen levels to 54%-60% at 4 hours, which generally reverts to about 80% after 24 hours. Plasminogen and alpha-2-antiplasmin decrease to 52%-70% and 25%-35% respectively after 4 hours and increase again to about 80% at 24 hours. A marked and prolonged decrease of the circulating fibrinogen level is only seen in a few patients.

In patients evaluated within four hours of onset of symptoms an occlusive thrombus is present in the infarct-related coronary artery in approximately 80% of patients experiencing a transmural myocardial infarction. In patients studied with coronary angiography prior to and following infusion of ACTILYSE, the use of ACTILYSE resulted in reperfusion of documented obstructed vessels within 90 minutes after the commencement of thrombolytic therapy in approximately 70% of the patients.

Treatment of myocardial infarction with ACTILYSE is intended to restore coronary artery patency, reduce infarct size, preserve ventricular function and reduce mortality.

Effect on Coagulation

ACTILYSE differs from other plasminogen activators in that it is fibrin-dependent. Relatively selective fibrinolysis with ACTILYSE, i.e. localised activation of the fibrinolytic system, is possible due to several factors such as the high affinity of tissue plasminogen activator for fibrin, the fibrin-dependent activation of tissue plasminogen activator, and the coprecipitation of plasminogen within the fibrin clot. As a result, ACTILYSE produces clot dissolution in vivo with minimal systemic effects.

Clinical Trials

Acute Myocardial Infarction (AMI)

Two ACTILYSE dose regimens have been studied in patients experiencing acute myocardial infarction. The comparative efficacy of these two regimens has not been evaluated.

Accelerated Infusion in AMI patients

Accelerated infusion of ACTILYSE was studied in an international, multi-centre trial (GUSTO) that randomised 41,021 patients with acute myocardial infarction to four thrombolytic regimens. Entry criteria included onset of chest pain within 6 hours of treatment and ST elevation of the ECG. The four regimens were:

- Streptokinase + subcutaneous heparin (n = 9841)
- Streptokinase + intravenous heparin (n = 10410)
- Accelerated alteplase + intravenous heparin (n = 10396), and
- Alteplase + streptokinase + intravenous heparin (n = 10374).

The accelerated alteplase dose was ≤ 100 mg over 90 minutes (see Section 4.2 Dose and Method of Administration).

The streptokinase (Kabikinase®) dose was 1.5 million units over 60 minutes.

Aspirin and heparin use were directed by the GUSTO protocol as follows:

- Aspirin: 160 mg (chewable) as soon as possible, followed by 160-325 mg daily.
- Heparin intravenous (IV): 5,000 units IV bolus as soon as possible, followed by 1,000 units per hour continuous IV infusion for at least 48 hours; subsequent heparin therapy was at the discretion of the attending physician.
- Heparin subcutaneous (SQ): 12,500 units four hours after initiation of streptokinase therapy, followed by 12,500 units twice daily for 7 days or until discharge, whichever came first. Many

patients randomised to SQ heparin received some IV heparin, usually in response to recurrent chest pain and or the need for a medical procedure. Some received IV heparin on arrival in the emergency room prior to enrolment and randomisation.

Results are given in the Table 1. The primary endpoint was 30-day mortality.

Table 1 GUSTO study Results

Event	*Accelerated Alteplase + IV Heparin*	*Streptokinase + IV Heparin*	*p-value*[1]	*Streptokinase + SQ Heparin*	*p-value*[1]
30-Day Mortality	6.3%	7.3%	0.003	7.3%	0.007
30-Day Mortality or Non-Fatal Stroke	7.2%	8.2%	0.006	8.0%	0.036
24-Hour Mortality	2.4%	2.9%	0.009	2.8%	0.029
Any Stroke	1.6%	1.4%	0.32	1.2%	0.03
Intracerebral Haemorrhage	0.7%	0.6%	0.22	0.5%	0.02

[1] Two-tailed p-value for comparison of accelerated alteplase with each streptokinase control arm.

Administration of 100 mg alteplase over 90 minutes, with concomitant IV heparin infusion, led to a lower mortality after 30 days (6.3%) as compared to the administration of streptokinase, 1.5 million IU over 60 minutes, with SQ or IV heparin (7.3%). The 1% absolute decrease in 30-day mortality for alteplase compared to streptokinase was statistically significant (p = 0.001).

There was a definite further reduction in mortality in the accelerated alteplase treated patients as compared to the patients treated with any of the three regimens using streptokinase. This improvement was independent of age, site of infarction, or area of infarction. This difference may be due to the higher patency rate achieved with accelerated alteplase in the acute patient with ST-segment elevation.

Alteplase-treated patients showed higher infarct related vessel patency rates at 90 minutes after thrombolysis than the streptokinase-treated patients. No differences in patency rates were noted at 180 minutes or longer.

ACTILYSE has been shown to reduce 30-day mortality in patients with acute myocardial infarction treated up to 12 hours after symptom onset.

A large scale mortality trial (ASSENT-2) in approximately 17,000 patients showed that alteplase and tenecteplase are therapeutically equivalent in reducing mortality (6.2% for both treatments, at 30 days). The use of tenecteplase was associated with a significantly lower incidence of non-intracranial bleedings compared to alteplase (26.4% versus 28.9%, p = 0.0003).

3-hour infusion in AMI patients

In patients studied in a controlled trial with coronary angiography at 90 and 120 minutes, following infusion of alteplase, infarct artery patency was observed in 71% and 85% of patients (n = 85), respectively. In a second study, where patients received coronary angiography prior to and following infusion of alteplase within 6 hours of the onset of symptoms, reperfusion of the obstructed vessel occurred within 90 minutes after the commencement of therapy in 71% of 83 patients.

In a double-blind, randomised trial (n = 138) comparing alteplase to placebo, patients infused with alteplase within 4 hours of onset of symptoms experienced improved left ventricular function at day 10 compared with placebo, when ejection fraction was measured by gated blood pool scan (53.2% versus 46.4%, P = 0.018). Relative to baseline values, the net changes in ejection fraction were +3.6% and -4.7% for the treated and placebo groups, respectively (P = 0.0001). Also documented was a reduced incidence of clinical congestive heart failure in the treated group (14%) compared to the placebo group (33%) (P = 0.009).

In a double-blind, randomised trial (n = 145) comparing alteplase to placebo, patients infused with alteplase within 2.5 hours of onset of symptoms experienced improved left ventricular function at a mean of 21 days compared to the placebo group, when ejection fraction was measured by gated blood pool scan (52% versus 48%, P = 0.08) and by contrast ventriculogram (61% versus 54%, P = 0.006). Although the contribution of alteplase alone is unclear, the incidence of nonischaemic cardiac

complications when taken as a group (i.e, congestive heart failure, pericarditis, atrial fibrillation, and conduction disturbance) was reduced when compared to those patients treated with placebo (P < 0.01).

In a double-blind, randomised trial (ASSET) (n = 5,013) comparing alteplase to placebo, patients infused with alteplase within 5 hours of the onset of symptoms of AMI experienced improved 30-day survival compared to those treated with placebo. At 1 month, the overall mortality rates were 7.2% for the alteplase group and 9.8% for the placebo group (P = 0.001). This benefit was maintained at 6 months for alteplase treated patients (10.4%) compared to those treated with placebo (13.1%, P = 0.008).

In a double-blind, randomised trial (n = 721) comparing alteplase to placebo, patients infused with alteplase within 5 hours of the onset of symptoms experienced improved ventricular function 10-22 days after treatment compared to the placebo group, when global ejection fraction was measured by contrast ventriculography (50.7% versus 48.5%, P = 0.01). Patients treated with alteplase had a 19% reduction in infarct size, as measured by cumulative release of HBDH (α-hydroxybutyrate dehydrogenase) activity compared to placebo-treated patients (P = 0.001). Patients treated with alteplase had significantly fewer episodes of cardiogenic shock (P = 0.02), ventricular fibrillation (P < 0.04) and pericarditis (P = 0.01) compared to patients treated with placebo. Mortality at 21 days in alteplase treated patients was reduced to 3.7% compared to 6.3% in placebo-treated patients (P = 0.05). Although these data do not demonstrate unequivocally a significant reduction in mortality for this study, they do indicate a trend that is supported by the results of the ASSET study.

In a randomised, double-blind study (LATE), 5,711 patients with symptoms of AMI received intravenous alteplase (100 mg over 3 hours) or matching placebo, between 6 and 24 hours from symptom onset. Both groups received immediate oral aspirin and for later recruits intravenous heparin for 48 hours. All patients were followed up for at least 6 months and 73% were followed up for 1 year. Intention-to-treat analysis of survival revealed a non-significant reduction in the alteplase group compared with placebo. 35-day mortality was 8.86% and 10.31% respectively, a relative reduction of 14.1% (95% CI: 0-28.1%, P = 0.07). Pre-specified survival analysis according to treatment within 12 hours of symptom onset, showed a significant reduction in mortality in favour of alteplase, 35-day mortality was 8.90% versus 11.97% for placebo, a relative reduction of 25.6% (95% CI: 6.3-45.0%, P = 0.0229). For patients admitted between 12 and 24 hours, the mortality after alteplase was 8.7% versus 9.2% (relative reduction of 5.4%, P = 0.14). This benefit was not significant overall but varied across subgroups.

Acute Massive Pulmonary Embolism

In a comparative randomised trial of alteplase versus urokinase in 63 patients with angiographically documented acute massive pulmonary embolism, patients were randomly assigned to treatment with either alteplase (10 mg as an intravenous bolus infusion, then 90 mg over 2 hours followed by heparin; n= 34) or urokinase (4,400 U/kg as an intravenous bolus infusion, then 4,400 U/kg per hour over 12 hours; n=29). Both treatment groups experienced a significant reduction in pulmonary embolism-induced pulmonary hypertension. Pulmonary haemodynamics improved significantly faster with alteplase than with urokinase. At 2 hours, total pulmonary resistance decreased by 36% in the alteplase group compared with 18% in the urokinase group (p = 0.0009). After 12 hours, the decrease in total pulmonary resistance was not statistically different between the treatment groups, 48% in the alteplase group versus 53% in the urokinase group.

There are no data available on survival following use of ACTILYSE in massive pulmonary embolism.

Acute Ischaemic Stroke

Several studies have been carried out in the field of acute ischaemic stroke. The NINDS study is the only study without an upper age limit, i.e. which also included patients over 80 years. All other randomised trials have excluded patients over 80 years of age. Therefore, treatment decisions in this patient group require particular care on an individual patient basis.

Meta-analysis of Stroke Studies

A meta-analysis of data from six placebo-controlled, double-blind trials was performed. The analysis was based on individual patient data from the ITT-population (n = 2,799) by means of a logistic regression model. The six trials included the NINDS (Parts 1 & 2), ECASS (I & II) and ATLANTIS (parts A & B) studies.

The objective of the meta-analysis was to study the comparability as well as to combine the data of the various trials of alteplase in acute ischaemic stroke and thereby to put the results of the NINDS Part 2 study into perspective (see '*NINDS Stroke Trials'* below).

An overview of these trials is presented in Table 2. With the exception of ECASS-I, the dose of alteplase used in the other studies was 0.9 mg/kg; a higher dose of alteplase of 1.1 mg/kg was used in the ECASS-I study. While the pivotal NINDS Part 1 & Part 2 studies examined the treatment window of 0-3 hours after onset of stroke symptoms, the other studies investigated an extended treatment window of up to 6 hours (after onset of stroke symptoms). With respect to patient selection, the inclusion and exclusion criteria were similar across the studies. The most relevant difference was that in ECASS (I & II) and ATLANTIS (Part B) studies, patients with major infarctions based on their CT scan (>1/3 of the middle cerebral artery territory) were excluded while this criterion was not applied in the NINDS studies.

Table 2 Meta-analysis: Alteplase Trials

STUDY	**NINDS**		**ECASS-I**	**ECASS-II**	**ATLANTIS**	
	Part 1	**Part 2**			**Part A**	**Part B**
Dosage	0.9 mg/kg (max. 90 mg)		1.1 mg/kg (max. 100 mg)	0.9 mg/kg (max. 90 mg)	0.9 mg/kg (max. 90 mg)	
Treatment Time Window	0-3 hrs		0-6 hrs	0-6 hrs	0-6 hrs	0-5 hrs
*Number of subjects treated within **0-3** hrs of onset (total number of subjects in each treatment group)*						
Alteplase	144	168	49 (313)	81 (409)	23 (372)	
Placebo	147	165	38 (307)	77 (391)	38 (383)	

The efficacy and safety results of the meta-analysis are summarised in Table 3. The results are presented as risk differences (RD) and as relative risks (RR) divided into subjects treated within 0-3 hrs of onset of stroke symptoms ('0-3 hrs') versus those treated between 3-6 hrs after onset of stroke symptoms ('3-6 hrs') and include the following endpoints (at day 90):

For efficacy:

- Functional independency, i.e. NIHSS 0-1
- Favourable outcome, i.e. modified Rankin Scale (mRS) 0-1
- Independent outcome, i.e. mRS 0-2

For safety:

- Disability or death, i.e. mRS 5-6
- Death (of all causes), i.e. mRS 6
- Intracerebral haemorrhage (ICH)
- Symptomatic ICH

Table 3 Meta-analysis: Summary of Efficacy and Safety Results

Outcome at day 90	0-3 hrs				3-6 hrs			
	Placebo	**Actilyse**	**RD^** (95% CI)	**RR^^** (95% CI)	**Placebo**	**Actilyse**	**RD^** (95% CI)	**RR^^** (95% CI)
EFFICACY								
NIHSS 0-1 Functional independency	108/465 23.2%	172/465 37.0%	14% (8, 20)	1.59 (1.30, 1.94)	275/921 29.9%	324/932 34.8%	5% (1, 9)	1.15 (1.01, 1.31)
mRS# 0-1 Favourable outcome	136/465 29.2%	197/465 42.4%	14% (7, 20)	1.47 (1.23, 1.76)	314/921 34.1%	346/932 37.1%	2% (-2, 6)	1.09 (0.97, 1.23)
mRS# 0-2 Independent outcome	185/465 39.8%	233/465 50.1%	11% (5, 17)	1.29 (1.12, 1.48)	424/921 46.0%	457/932 49.0%	2% (-2, 7)	1.07 (0.97, 1.17)
SAFETY								
mRS# 5-6 Disability or death	117/465 25.2%	112/465 24.1%	-1% (-7, 4)	0.96 (0.77, 1.19)	189/921 20.5%	226/932 24.2%	3% (0, 7)	1.18 (1.03, 1.36)
mRS# 6 Death (of all causes)	80/465 17.2%	82/465 17.6%	1% (-4, 5)	0.97 (0.73, 1.29)	99/921 10.7%	132/932 14.2%	3% (0, 6)	1.32 (1.03, 1.68)
ICH Intracerebral haemorrhage	147/465 31.6%	158/465 34.0%	2% (-4, 8)	1.01 (0.85, 1.22)	220/921 23.9%	317/932 34.0%	11% (7, 14)	1.31 (1.14, 1.50)
Symptomatic ICH	7/427 1.6%	33/416 7.9%	6% (3, 9)	4.03 (1.85, 8.79)	14/654 2.1%	56/671 8.3%	6% (4, 8)	3.58 (2.02, 6.34)

#mRS: 0 = no symptoms; 1 = no significant disability; 5 = severe disability; 6 = death

^RD = Risk Difference. ^^RR = Relative Risk.

The meta-analysis of all patients treated within 3 hours after stroke onset confirmed the beneficial effect of alteplase as observed in the NINDS Part 2 study. In this analysis, the probability of a favourable outcome at day 90 increased as the time to treatment with alteplase decreased. The risk difference versus placebo for a good recovery (favourable outcome) was approximately 14% despite an increased risk of symptomatic intracranial haemorrhage (see Table 3). A symptomatic intracranial haemorrhage rate (parenchymal haematoma, type II) was seen in 5.9% of patients treated with alteplase versus 1.1% with placebo ($p<0.0001$). The data do not allow drawing a definite conclusion on the treatment effect on death. The point estimate for the relative risk of death suggests that it is similar between the alteplase and placebo groups (RR=0.97, 95% CI = [0.73-1.29]). The meta-analysis also showed that alteplase 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.

In conclusion, the benefit/risk of alteplase, when given within 3 hours of stroke onset and taking into account the precautions stated, is considered favourable. This analysis confirms that rapid treatment with alteplase is associated with better outcomes at day 90. It also provides evidence that the therapeutic window may extend as far out as 4.5 hours (which was later confirmed by the results of the ECASS III trial – see below).

NINDS Stroke Trials

The pivotal NINDS Part 1 and Part 2 trials enrolled acute ischaemic stroke patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computerised tomography (CT) scan was performed prior to treatment to rule out the presence of intracranial haemorrhage. Patients were also excluded for the presence of conditions related to risks of bleeding, for minor neurological deficit, for rapidly improving symptoms prior to initiating study treatment, or for blood glucose of < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L) (see Section 4.3 Contraindications). Patients were randomised to receive either 0.9 mg/kg alteplase (maximum of 90 mg), or placebo. Alteplase was administered as a 10% initial bolus over 1 minute followed by continuous intravenous infusion of the remainder over 60 minutes.

The initial study NINDS Part 1 (n = 291, ITT-analysis) evaluated neurological improvement at 24 hours after stroke onset. The primary endpoint, the proportion of patients with a 4 or more point improvement in the National Institutes of Health Stroke Scale (NIHSS) score or complete recovery (NIHSS score = 0), was not significantly different between treatment groups. A secondary analysis

demonstrated a significantly superior 3-month outcome associated with alteplase treatment using the following stroke assessment scales: Barthel Index (score ≥ 95), Modified Rankin Scale (score ≤ 1), Glasgow Outcome Scale (score = 1), and the NIHSS (score ≤ 1).

A second study NINDS Part 2 (n = 333, ITT-analysis) assessed clinical outcome at 3 months as the primary outcome. A favourable outcome was a priori defined as minimal or no disability using the four stroke assessment scales: Barthel Index (score ≥ 95), Modified Rankin Scale (score ≤ 1), Glasgow Outcome Scale (score = 1), and NIHSS (score ≤ 1). The results comparing alteplase and placebo-treated patients for the four outcome scales together (Generalised Estimating Equations) and individually are presented in Table 4. In this study, depending upon the scale, the favourable outcome of minimal or no disability occurred in at least 11 per 100 more patients treated with alteplase than those receiving placebo. The odds ratio for favourable outcome in the alteplase group was 1.7 (95% CI = 1.2 - 2.6). Compared to placebo there was 13% absolute increase in the number of patients with minimal or no disability (mRS 0-1) (OR =1.7; 95% CI = 1.1 - 2.6). There was also a consistent benefit seen with alteplase on other neurologic and disability scales (see Table 4). Secondary analyses demonstrated consistent functional and neurological improvement within all four stroke scales as indicated by median scores. These results were highly consistent with the 3-month outcome treatment effects as observed in the Part 1 study.

Table 4 The NINDS rt-PA Stroke Trial, Part 2: *3-Month Efficacy Outcomes*

Analysis	*Frequency of Favourable Outcome*[a]				
	Placebo (n = 165)	*Alteplase (n = 168)*	*Absolute Difference (95% CI)*	*Relative Frequency*[b] *(95% CI)*	*p-Value*[c]
Generalised Estimating Equations (Multivariate)	-	-	-	1.34 (1.05, 1.72)	0.02
Barthel Index	37.6%	50.0%	12.4% (3.0, 21.9)	1.33 (1.04, 1.71)	0.02
Modified Rankin Scale	26.1%	38.7%	12.6% (3.7, 21.6)	1.48 (1.08, 2.04)	0.02
Glasgow Outcome Scale	31.5%	44.0%	12.5% (3.3, 21.8)	1.40 (1.05, 1.85)	0.02
NIHSS	20.0%	31.0%	11.0% (2.6, 19.3)	1.55 (1.06, 2.26)	0.02

[a] *Favourable Outcome is defined as recovery with minimal or no disability.*

[b] *Value > 1 indicates frequency of recovery in favour of alteplase treatment.*

[c] *p-Value for Relative Frequency is from Generalised Estimating Equations with log link.*

The incidences of all-cause 90-day mortality, ICH, and new ischaemic stroke following alteplase treatment compared to placebo are presented in Table 5 as a combined safety analysis (n = 624) for Parts 1 and 2. These data indicated a significant increase in ICH following alteplase treatment, particularly symptomatic ICH within 36 hours. However, in alteplase-treated patients, there were no increases compared to placebo in the incidences of 90-day mortality or severe disability.

Table 5 The NINDS rt-PA Stroke Trial: *3-Month Safety Outcome*

	Part 1 and Part 2 Combined		
	Placebo (n = 312)	*Alteplase (n = 312)*	*p-Value***
All-Cause 90-day Mortality	64 (20.5%)	54 (17.3%)	0.36
Total ICH*	20 (6.4%)	48 (15.4%)	< 0.01
Symptomatic	4 (1.3%)	25 (8.0%)	< 0.01
Asymptomatic	16 (5.1%)	23 (7.4%)	0.32
Symptomatic ICH within 36 hours	2 (0.6%)	20 (6.4%)	< 0.01
New Ischaemic Stroke (3-months)	17 (5.4%)	18 (5.8%)	1.00

* *Within trial follow-up period. Symptomatic ICH was defined as the occurrence of sudden clinical worsening followed by subsequent verification of ICH on CT scan. Asymptomatic ICH was defined as ICH detected on a routine repeat CT scan without preceding clinical worsening.*

** *Fisher's Exact Test*

In a pre-specified subgroup analysis in patients receiving aspirin prior to onset of stroke symptoms, there was preserved favourable outcome for alteplase-treated patients.

Exploratory, multivariate analyses of both studies combined (n = 624) to investigate potential predictors of ICH and treatment effect modifiers were performed. In alteplase-treated patients presenting with severe neurological deficit (e.g. NIHSS > 25) or of advanced age (e.g. > 80 years of age), the trends toward increased risk for symptomatic ICH within the first 36 hours were more prominent. Similar trends were also seen for total ICH and for all-cause 90-day mortality in these patients. When risk was assessed by the combination of death and severe disability in these patients, there was no difference between placebo and alteplase groups. Analyses for efficacy suggested a reduced but still favourable clinical outcome for alteplase-treated patients with severe neurological deficit or advanced age at presentation.

SITS-MOST Study

In a large observational study (SITS-MOST: The Safe Implementation of Thrombolysis in Stroke – Monitoring Study), the safety and efficacy of alteplase for acute stroke treatment within 3 hours in a routine clinical setting was assessed and compared with results from randomised clinical trials. All patients had to be compliant with the Product Information of ACTILYSE. Treatment and outcome data of 6,483 patients from 285 centres in 14 European countries were collected. Primary outcomes were symptomatic intracranial haemorrhage within 24 hours and mortality at 3 months. The rate of symptomatic intracranial haemorrhage (as per NINDS definition) found in SITS-MOST was comparable with the symptomatic intracranial haemorrhage rate as reported in randomised trials, 7.3% (468/6437; 95% CI = 6.7 - 7.9) in SITS-MOST versus 8.6% (40/465; 95% CI = 6.3 - 11.6) in randomised clinical trials. Mortality was 11.3% (701/6218; 95% CI = 10.5 - 12.1) in SITS-MOST versus 17.3% (83/479; 95% CI = 14.1 - 21.1) in randomised clinical trials. The results of SITS-MOST indicate that, the routine clinical use of alteplase within 3 hours of stroke onset is as safe as reported in randomised clinical trials.

ECASS III Trial

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. The study enrolled patients with measurable neurological deficit compliant with the Product Information of ACTILYSE except the time-window. After exclusion of brain haemorrhage or major infarction by computed tomography and/or as assessed clinically (e.g. NIHSS > 25), patients with acute ischemic stroke were randomised in a 1:1 double-blind fashion to intravenous alteplase (0.9 mg/kg bodyweight) or placebo. The primary endpoint was disability at 90 days, dichotomised for favourable (modified Rankin scale [mRS] 0 to 1) or unfavourable (mRS 2 to 6) outcome. The principal secondary endpoint was a global outcome analysis of four neurologic and disability scores combined. Safety endpoints included mortality, any intracranial haemorrhage, symptomatic intracranial haemorrhage, and serious adverse events.

A total of 821 patients (418 alteplase/403 placebo) were randomised. Of the 730 patients (375 alteplase/355 placebo) treated, the age ranged between 20 to 80 years of age, 68.8% aged between 61 and 80 years. More patients achieved favourable outcome with alteplase (52.4%) versus placebo (45.2%; odds ratio [OR] = 1.3; 95% CI = 1.02 - 1.76; relative risk [RR] = 1.16; 95% CI = 1.01 - 1.34; p = 0.038). On the global analysis, outcome was also improved (OR = 1.28; 95% CI = 1.00 - 1.65; p = 0.048). The incidence of intracranial haemorrhage was higher with alteplase versus placebo (any ICH 27.0% versus 17.6%, p = 0.0012; symptomatic ICH by NINDS definition 7.9% versus 3.5%, p = 0.006). Haemorrhagic transformations were seen in 22.24% of patients in the alteplase group versus 16.13% in the placebo group. Parenchymatous haemorrhages occurred in 4.78% with alteplase versus 1.49% with placebo. Mortality was low and not significantly different between alteplase (7.7%) and placebo (8.4%; p = 0.681). There were 3 cases of fatal intracranial haemorrhages in the alteplase group, none with placebo. The results of ECASS III show that alteplase between 3 and 4.5 hours after symptom onset significantly improves clinical outcomes in patients with acute ischemic stroke. See Table 6.

Since generally, the net clinical benefit for alteplase decreases over time, the benefits and risks need to be carefully weighed and earlier treatment increases the probability of a favourable outcome. Pooled data demonstrate that the net-clinical benefit is no longer favourable for alteplase in the time window beyond 4.5 hours.

Table 6 ECASS III Trial: Summary of Main Efficacy and Safety Outcomes

Outcomes at day 90		Placebo	Actilyse	Odds Ratio (95% CI)	Relative Risk (95% CI)	p-value
EFFICACY						
mRS 0-1 Favourable outcome		182/403 (45.2%)	219/418 (52.4%)	1.34 (1.02, 1.76)	1.16 (1.01, 1.34)	0.038
SAFETY						
All cause mortality		34/403 (8.4%)	32/418 (7.7%)	0.90 (0.54, 1.76)	0.91 (0.57, 1.44)	0.681
Any ICH		71/403 (17.6%)	113/418 (27.0%)	1.72 (1.24, 2.42)	1.53 (1.18, 2.00)	0.001
Symptomatic ICH by definition[a]	ECASS III	1/403 (0.2%)	10/418 (2.4%)	9.85 (1.26, 77.32)	9.64 (1.24, 74.97)	0.008
	ECASS II	9/403 (2.2%)	22/418 (5.3%)	2.43 (1.11, 5.35)	2.36 (1.10, 5.06)	0.023
	NINDS	14/403 (3.5%)	33/418 (7.9%)	2.38 (1.25, 4.52)	2.27 (1.23, 4.18)	0.006
	SITS-MOST	1/403 (0.2%)	8/418 (1.9%)	7.84 (0.98, 63.00)	7.71 (0.97, 61.39)	0.022

[a] *Definitions of symptomatic ICH:*

ECASS III definition – Symptomatic cerebral haemorrhage was defined as any blood in the brain or intracranially associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the haemorrhage has been identified as the dominating cause of the neurologic deterioration.

ECASS II definition – Any intracranial bleed and 4 points or more worsening on the NIHSS score from baseline or the lowest value in the first 7 days, or any haemorrhage leading to death.

NINDS definition – A haemorrhage was considered symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of haemorrhage or any decline in neurologic status. To detect intracranial haemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical finding suggested haemorrhage.

SITS-MOST definition – Local or remote parenchymal haematoma type 2 on the 22- to 36-hour post-treatment imaging scan, combined with a neurologic deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.

Use in the Elderly

Data of patients over 80 years of age are very limited. A pooled analysis was performed on the available data from six randomised controlled clinical trials (NINDS Parts 1 & 2, ATLANTIS Parts A & B, ECASS II & III) involving 137 patients aged ≥ 80 years treated within the 0-4.5 hour period.

The pooled analysis showed that the absolute risk difference between alteplase and placebo for a favourable outcome (mRS 0-1) at day 90 was 1.4% and for independence (mRS 0-2) at day 90 was 2.1%, which was not statistically significant. A greater absolute difference of 8.1% for favourable outcome (mRS 0-1) and 10.1% for independence (mRS 0-2) was observed in favour of alteplase compared to placebo in the subgroup excluding patients with severe stroke at baseline (NIHSS ≥ 20), however the treatment difference was not statistically significant. In the small subgroup of patients with severe stroke (n=48), the functional outcome was very poor.

Efficacy was reduced in patients over 80 years of age compared to younger patients. A favourable outcome (mRS 0-1) at day 90 was seen in 27.63% (n=21/76) of the patients aged ≥ 80 years treated with alteplase compared to 46.03% (n=470/1021) of patients aged < 80 years (OR alteplase over placebo combined for both age groups and adjusted for NIHSS at baseline = 1.43; 95% CI = 1.18 - 1.74). Excluding those patients with severe stroke, a favourable outcome (mRS 0-1) at day 90 was seen in 44.4% (n=20/45) of the patients aged ≥ 80 years treated with alteplase compared to 52.2% (n=443/849) of patients aged < 80 years (OR alteplase over placebo combined for both age groups and adjusted for NIHSS at baseline = 1.39; 95% CI = 1.13 - 1.70).

All-cause mortality was 27.6% (n=21/76) on alteplase versus 23% (n=14/61) on placebo in the group of patients aged ≥ 80 years (OR adjusted for NIHSS at baseline = 0.96; 95% CI = 0.36 - 2.59); compared to 10.2% (n=104/1021) on alteplase versus 11.5% (n=120/1041) on placebo in the group of younger patients aged < 80 years.

Any ICH was significantly higher on alteplase (51.3%; n=39/76) versus placebo (21.3%; n=13/61) in patients aged ≥ 80 years (OR adjusted for NIHSS at baseline = 4.01; 95% CI = 1.76 - 9.13)

compared to those < 80 years of age (28.9%; n=295/1021 on alteplase versus 23.5%; n=245/1041 on placebo).

Symptomatic ICH (as per SITS-MOST definition) was significantly higher on alteplase (6.6%; n=5/76) versus placebo (0%; n=0/61) in patients aged ≥ 80 years (unadjusted OR = 8.51; 95% CI = 0.45 - 159.02) compared to those < 80 years of age (2.5%; n=25/1021 on alteplase versus 0.5%; n=5/1041 on placebo).

5.2 PHARMACOKINETIC PROPERTIES

ACTILYSE is cleared rapidly from circulating plasma primarily by the liver, at a rate of approximately 500 mL/min in patients with vascular disease, and approximately 700 mL/min in normal subjects. More than 50% of ACTILYSE present in plasma is cleared within 5 minutes after the infusion has been terminated, and approximately 80% is cleared within 10 minutes. For the residual amount remaining in a deep compartment, a beta half-life of about 40 minutes was measured.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies with ACTILYSE have not been performed to determine genotoxicity.

Carcinogenicity

Studies with ACTILYSE have not been performed to determine carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are: arginine, phosphoric acid, polysorbate 80, and nitrogen. Phosphoric acid and/or sodium hydroxide may be used prior to lyophilisation for pH adjustment.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Lyophilised ACTILYSE is stable up to the expiration date stamped on the vial.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 24 hours at 2-8°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.

Protect the lyophilised material during storage from light. During the period of reconstitution and infusion, protection from light is not necessary.

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)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use in only one patient. Discard any unused solution.

6.7 PHYSICOCHEMICAL PROPERTIES

ACTILYSE is a tissue plasminogen activator produced by recombinant DNA technology. It is a purified fibrinolytic glycoprotein of 527 amino acids, synthesised using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator. The manufacturing process involves the secretion of the serine protease t-PA into the culture medium by an established mammalian cell line into which the cDNA for tissue plasminogen activator has been genetically inserted.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

26 September 1991

10 DATE OF REVISION

17 October 2023

Summary table of changes

Section changed	Summary of new information
4.2	Update to dosing table for AIS and administration wording, updated pictures in instructions for reconstituting ACTILYSE table, editorial changes
4.3 & 4.4	Updated to remove gentamicin hypersensitivity warning, editorial changes