ACTILYSE®
(Alteplase)

NAME OF THE MEDICINE

ACTILYSE (alteplase, recombinant tissue plasminogen activator, rt-PA).

DESCRIPTION

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.

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

PHARMACOLOGY

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.

Pharmacokinetics

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.

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 DOSAGE AND 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.

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 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 (11.1, 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=0/0) 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).

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.

CONTRAINDICATIONS

ACTILYSE should not be administered to patients with known hypersensitivity to alteplase, gentamicin (a trace residue from the manufacturing process) or any of the excipients (listed under PRESENTATION).

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 (INR> 1.3), see PRECAUTIONS, Bleeding

Additional Contraindications for Patients with Acute Myocardial Infarction / 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
- 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.

For use in patients over 80 years of age, see PRECAUTIONS – Additional Warnings in Acute Ischaemic Stroke.

PRECAUTIONS

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 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.

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 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 OVERDOSAGE.

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 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 / Pulmonary Embolism:

Additionally, the potential risks of ACTILYSE therapy should be carefully evaluated against the expected benefits in patients treated for acute Myocardial Infarction / 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 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 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 DOSAGE AND 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 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 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.

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

- Any situations involving a high risk of haemorrhage (see CONTRAINDICATIONS)
- Small asymptomatic aneurysms of the cerebral vessels
- Late time-to-treatment onset
- Patients pre-treated with aspirin 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.
- Patients over 80 years of age have an increased risk of haemorrhage (both ICH and symptomatic ICH), mortality and decreased efficacy compared to younger patients (see CLINICAL TRIALS), reducing the net benefit from treatment compared to young patients. Therefore, the use of ACTILYSE should be weighed carefully against anticipated risks on an individual patient basis.

ACTILYSE treatment should not be initiated later than 4.5 hours after the onset of stroke symptoms (see 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 (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.

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

In patients with very mild stroke, the risks outweigh the expected benefit (see CONTRAINDICATIONS).

Patients with very severe stroke are at higher risk of intracerebral haemorrhage and death and should not be treated with ACTILYSE (see 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 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 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 CLINICAL TRIALS). Patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L) at baseline should not be treated with ACTILYSE (see CONTRAINDICATIONS).

Reperfusion of 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 ACTILYSE (see DOSAGE AND ADMINISTRATION).

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 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 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

There has been little experience with re-administration of ACTILYSE. Re-administration should be undertaken with caution. Less than 0.5% of patients receiving single courses of ACTILYSE therapy have experienced transient antibody formation. No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systemic experience with re-administration of ACTILYSE. Anaphylactoid reactions associated with the administration of ACTILYSE are rare and can be caused by hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. The stopper of the glass vial with ACTILYSE powder contains natural rubber (a derivative of latex) which may cause allergic reactions. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment should be initiated.

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 breastfeeding women.

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.

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 CLINICAL TRIALS). For use in patients above 80 years of age, see PRECAUTIONS.

Genotoxicity

Studies with ACTILYSE have not been performed to determine genotoxicity.

Carcinogenicity

Studies with ACTILYSE have not been performed to determine carcinogenicity.

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.

Effects on ability to drive and use machines

Not applicable.

INTERACTIONS WITH OTHER MEDICINES

The risk of haemorrhage may be increased with the use of coumarin derivatives, antiplatelet aggregation agents, heparin or any other agent which influences haemostasis (before, during or within the first 24 hours after treatment with ACTILYSE). The concomitant use of GP IIb/IIIa antagonists increases the risk of bleeding.

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.

Concomitant treatment with Angiotensin Converting Enzymes (ACE) inhibitors may enhance the risk of suffering an anaphylactoid reaction (see ADVERSE EFFECTS). Monitoring is recommended particularly for patients receiving concomitant ACE inhibitors.

ADVERSE EFFECTS

The most frequent adverse reaction associated with ACTILYSE is bleeding (>1%, ≤10% major bleeds; >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 pulmonary embolism and stroke (within the 0 - 4.5 hours time window) is smaller than the number in trials for myocardial infarction (see CLINICAL TRIALS). Except for intracranial haemorrhage as side effect in the stroke indication as well as for reperfusion arrhythmias in the 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 myocardial infarction indication only):

>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

Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional anti-arrhythmic therapies.

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

>0.1% and ≤1%: intracranial haemorrhage, such as

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

– subarachnoid haemorrhage

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

>1% and ≤10%: intracranial haemorrhage, such as

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

Symptomatic intracerebral haemorrhages represents the major adverse events (up to 10% of patients). However, this had not shown an increased overall morbidity or mortality.

b) Adverse events related to all three indications

Gastrointestinal disorders:

>1% and ≤10%: gastrointestinal haemorrhage, such as

– gastric haemorrhage
– gastric ulcer haemorrhage
– rectal haemorrhage
– haematemesis
– melaena
– mouth haemorrhage
– nausea
– vomiting

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

>0.1% and ≤1%: retroperitoneal haemorrhage, such as

– retroperitoneal haematoma
– gingival bleeding

General disorders and administration site conditions:

>10%: injection site haemorrhage, puncture site haemorrhage, such as

– catheter site haematoma
– catheter site haemorrhage

Immune system disorders:

>0.1% and ≤1%: 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

If they occur, conventional anti-allergic therapy should be initiated. In the cases reported, a relatively larger proportion of patients were receiving concomitant ACE inhibitors. No definite anaphylactic (IgE mediated) reactions to ACTILYSE are known. Transient antibody formation to ACTILYSE has been observed in rare cases and with low titres, but a clinical relevance of this finding could not be established.

Injury and poisoning and procedural complications

>0.01% and ≤0.1%: fat embolism, which may lead to corresponding consequences in the organs concerned

The classification of fat embolism, which was not observed in the clinical trial population, was based on spontaneous reporting.

Eye disorders:

≤0.01%: eye haemorrhage

Cardiac disorders:

>0.1% and ≤1%: pericardial haemorrhage

Investigations:

>10%: blood pressure decreased

>1% and ≤10%: body temperature increased

Renal and urinary disorders:

>1% and ≤10%: urogenital haemorrhage, such as
- haematuria
- haemorrhage urinary tract

Respiratory, thoracic and mediastinal disorders:

>1% and ≤10%: respiratory tract haemorrhage, such as
- pharyngeal haemorrhage
- haemoptysis
- epistaxis

Surgical and medical procedures:

>1% and ≤10%: transfusion

Skin and subcutaneous tissue disorders:

>1% and ≤10%: ecchymosis

Vascular disorders:

>10%: haemorrhage (such as haematoma)

>0.1% and ≤1%: embolism, which may lead to corresponding consequences in the organs concerned

>0.01% and ≤0.1%: bleeding of parenchymatous organs, such as
- hepatic haemorrhage
- pulmonary 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 pulmonary embolism: pulmonary re-embolisation, pulmonary oedema, pleural effusion, hypotension

Use in acute ischemic stroke: cerebral oedema, cerebral herniation, seizure, new ischemic stroke

DOSAGE AND ADMINISTRATION

Administer ACTILYSE as soon 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 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*.

Myocardial Infarction

a) Accelerated Infusion

The accelerated dosage regimen is based on the results from the GUSTO Study (See PHARMACOLOGY).

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

- 15 mg intravenous bolus
- 50 mg infusion over the first 30 minutes
- 35 mg infusion over the following 60 minutes.

For patients weighing less than or equal to 65 kg, the dose is adjusted on the basis of bodyweight as follows:

- 15 mg intravenous bolus
- 0.75 mg/kg infusion over the first 30 minutes
- 0.5 mg/kg infusion over the following 60 minutes.

b) 3 Hour Infusion

For a description of the trials this dosage regimen is based on, see PHARMACOLOGY.

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

- 10 mg intravenous bolus
- 50 mg infusion over the first hour
- 40 mg infusion over the following 2 hours.

For patients weighing less than or equal to 65 kg, the dose is adjusted on the basis of bodyweight so that the total dose does not exceed 1.5 mg/kg.

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 CLINICAL TRIALS.

Pulmonary Embolism

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,
- 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 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 PRECAUTIONS – Additional Warnings in Acute Ischaemic Stroke)

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

Treatment with ACTILYSE should be initiated as early as possible within 4.5 hours of symptom onset. The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Adjunctive therapy:

The safety and efficacy of this regimen with concomitant administration of heparin and aspirin within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of aspirin 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.

Reconstitution

Do not use vial if vacuum is not present.

ACTILYSE should be reconstituted to a concentration of 1 mg alteplase per mL by aseptically adding the appropriate volume of sterilised Water for Injections into the ACTILYSE dry powder vial:

ACTILYSE 10 mg vial

- Reconstitute the ACTILYSE 10 mg vial with 10 mL sterilised Water for Injections in the accompanying vial.
- Reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterilised Water for Injections into the lyophilised cake.
- When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

ACTILYSE 20 mg vial

- Reconstitute the ACTILYSE 20 mg vial with 20 mL sterilised Water for Injections in the accompanying vial by use of the transfer cannula (provided with the pack). The transfer cannula must always be introduced vertically into the stopper and through the mark at its centre.
- As an alternative to the use of the transfer cannula, reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterilised Water for Injections into the lyophilised cake.
- When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

ACTILYSE 50 mg vial

- Reconstitute the ACTILYSE 50 mg vial with 50 mL sterilised Water for Injections in the accompanying vial by use of the transfer cannula (provided with the pack). The transfer cannula must always be introduced vertically into the stopper and through the mark at its centre.
- As an alternative to the use of the transfer cannula, reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterilised Water for Injections into the lyophilised cake.
- When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

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.

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 dilution of the 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.

OVERDOSAGE

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

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.

PRESENTATION AND STORAGE CONDITIONS

ACTILYSE 10 mg

Box containing 1 vial of ACTILYSE 10 mg 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 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 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.

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

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.

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

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

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 September 1991

DATE OF MOST RECENT AMENDMENT

6 July 2015