NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ACTILYSE 10 mg powder and solvent for solution for injection and infusion
ACTILYSE 20 mg powder and solvent for solution for injection and infusion
ACTILYSE 50 mg powder and solvent for solution for injection and infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTILYSE 10 mg
1 vial contains: 10 mg alteplase in 466.6 mg dry substance
1 vial of solvent contains: 10 mL sterilised water for injection.

ACTILYSE 20 mg
1 vial contains: 20 mg alteplase in 933.2 mg dry substance
1 vial of solvent contains: 20 mL sterilised water for injection.
(Not marketed)

ACTILYSE 50 mg
1 vial contains: 50 mg alteplase in 2333 mg dry substance
1 vial of solvent contains: 50 mL sterilised water for injection.

Alteplase is produced by recombinant DNA technique using a Chinese hamster ovary cell-line. The specific activity of alteplase in-house reference material is 580,000 IU/mg. This has been confirmed by comparison with the second international WHO standard for t-PA. The specification for the specific activity of alteplase is 522,000 to 696,000 IU/mg.

For the full list of excipients, see section 6.1.

The reconstituted solution contains 1 mg alteplase per mL.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion.

The powder is presented as a colourless to pale yellow lyophilisate cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute Myocardial Infarction

ACTILYSE is indicated for fibrinolytic therapy in acute thrombotic artery occlusion to restore coronary artery patency, reduce infarct size, preserve ventricular function, prevent cardiac insufficiency and reduce mortality.

- 90 minutes (accelerated) dose regimen (see section 4.2): for patients in whom treatment can be started within 6 h of symptom onset;
- 3 hour dose regimen (see section 4.2): for patients in whom treatment can be started between 6 - 12 hrs after symptom onset.

Acute Massive Pulmonary Embolism

ACTILYSE is also indicated in patients with acute massive pulmonary embolism accompanied by haemodynamic instability.

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

Acute Myocardial Infarction

ACTILYSE should be administered as early as possible after the onset of symptoms. A total dose of 100 mg should not be exceeded.

a) Accelerated (90 minute) dose regimen for patients with acute myocardial infarction, in whom treatment can be started within 6 hours of symptom onset.

In patients with a body weight ≥ 65 kg:
- 15 mg as an intravenous bolus, immediately followed by
- 50 mg as an intravenous infusion over the first 30 minutes, followed by an intravenous infusion of
- 35 mg over 60 minutes, until the maximum dose of 100 mg has been administered.

In patients with a body weight < 65 kg the total dose should be weight adjusted with:-
- 15 mg as an intravenous bolus, immediately followed by
- 0.75 mg/kg bodyweight as an intravenous infusion over the first 30 minutes (maximum 50 mg), followed by an intravenous infusion of 0.5 mg/kg over 60 minutes (up to a maximum of 35 mg).

b) 3 hour dosage regimen for patients with acute myocardial infarction, in whom treatment can be started between 6 and 12 hours after symptom onset.

In patients with a body weight ≥ 65 kg
- 10 mg as an intravenous bolus, immediately followed by
- 50 mg as an intravenous infusion over the first hour, followed by an intravenous infusion of
- 40 mg for the next 2 hours, until the maximum dose of 100 mg has been administered.

In patients with a bodyweight < 65 kg:
- 10 mg as an intravenous bolus, immediately followed by
- an intravenous infusion up to a maximum total dose of 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.

Acute Massive Pulmonary Embolism

In patients with a body weight ≥ 65 kg:
A total dose of 100 mg should be administered in 2 hours. The recommended dose regimen is:
- 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 has been administered.

In patients with a body weight < 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.

Adjunctive Therapy

After treatment with ACTILYSE, heparin therapy should be initiated (or resumed) when aPTT values are less than twice the upper limit of normal. The infusion should be adjusted to maintain aPTT between 50 - 70 seconds (1.5 to 2.5 fold of the reference value).

Acute Ischaemic stroke

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

Treatment should be initiated as early as possible within 4.5 hours of symptom onset (see section 4.4). 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)	Infusion Administration (50 mL Syringes, 1 mg/mL concentration)		
				1st Syringe	2nd Syringe	Infusion Rate* (mL/hour)
40	36.0	3.6	32.4	32.4	N/A	32.4
42	37.8	3.8	34.0	34.0	N/A	34.0
44	39.6	4.0	35.6	35.6	N/A	35.6
46	41.4	4.1	37.3	37.3	N/A	37.3
48	43.2	4.3	38.9	38.9	N/A	38.9
50	45.0	4.5	40.5	40.5	N/A	40.5
52	46.8	4.7	42.1	42.1	N/A	42.1
54	48.6	4.9	43.7	43.7	N/A	43.7
56	50.4	5.0	45.4	45.4	N/A	45.4
58	52.2	5.2	47.0	47.0	N/A	47.0
60	54.0	5.4	48.6	48.6	N/A	48.6
62	55.8	5.6	50.2	50.2	N/A	50.2
64	57.6	5.8	51.8	50.0	1.8	51.8
66	59.4	5.9	53.5	50.0	3.5	53.5
68	61.2	6.1	55.1	50.0	5.1	55.1
70	63.0	6.3	56.7	50.0	6.7	56.7
72	64.8	6.5	58.3	50.0	8.3	58.3
74	66.6	6.7	59.9	50.0	9.9	59.9
76	68.4	6.8	61.6	50.0	11.6	61.6
78	70.2	7.0	63.2	50.0	13.2	63.2
80	72.0	7.2	64.8	50.0	14.8	64.8
82	73.8	7.4	66.4	50.0	16.4	66.4
84	75.6	7.6	68.0	50.0	18.0	68.0
86	77.4	7.7	69.7	50.0	19.7	69.7
88	79.2	7.9	71.3	50.0	21.3	71.3
90	81.0	8.1	72.9	50.0	22.9	72.9
92	82.8	8.3	74.5	50.0	24.5	74.5
94	84.6	8.5	76.1	50.0	26.1	76.1
96	86.4	8.6	77.8	50.0	27.8	77.8
98	88.2	8.8	79.4	50.0	29.4	79.4
100+	90.0	9.0	81.0	50.0	31.0	81.0

* Infusion rate is the same for both the first and second syringes.

Adjunctive therapy

The safety and efficacy of this regimen with concomitant administration of heparin or platelet aggregation inhibitors such as acetylsalicylic acid during the first 24 hours after the symptom-onset has not been investigated sufficiently. Therefore, administration of intravenous heparin or platelet aggregation inhibitors such as acetylsalicylic acid should be avoided in the first 24 hours after treatment with ACTILYSE due to 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.

Notes:

a) For exact dosing, administration of ACTILYSE with an infusion pump is preferable, however, a gravity infusion set can be used instead.

b) To give the patient the maximum benefit of ACTILYSE, residual volume remaining in intravenous application devices should be kept to a minimum.

Method of administration

The reconstituted solution should be administered intravenously and is for immediate use.

4.3 Contraindications

ACTILYSE is contraindicated in

- patients with known hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients
- cases where there is a high risk of haemorrhage such as:
  - significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
  - patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (INR > 1.3) (see section 4.4, subsection “Bleeding”)
  - any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
  - history or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
  - severe uncontrolled arterial hypertension
  - major surgery or significant trauma in the past 10 days, (this includes any trauma associated with the current acute myocardial infarction), recent trauma to head or cranium
  - prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery within the past 10 days, recent puncture of a non-compressible blood vessel (e.g. subclavian or jugular vein puncture)
  - severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
  - bacterial endocarditis, pericarditis
  - acute pancreatitis
  - documented ulcerative gastrointestinal disease during the last 3 months
  - arterial aneurysms, arterial / venous malformations
  - neoplasm with increased bleeding risk

Additional contraindications in acute myocardial infarction and 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 in 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
- symptoms of acute ischaemic stroke that were either rapidly improving or only minor before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques
- seizure at the onset of stroke
- history of previous stroke or serious head-trauma within three months
- a combination of previous stroke and diabetes mellitus
- administration of heparin within 48 hours preceding the onset of stroke with an elevated activated partial thromboplastin time (aPTT) at presentation
- platelet count of less than 100,000 / mm^3
- systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg, or aggressive management (IV medication) necessary to reduce blood pressure to these limits
- blood glucose < 50 mg/dL or > 400 mg/dL
- children and adolescents under 18 years of age

4.4 Special warnings and precautions for use

The appropriate presentation of alteplase product should be chosen carefully and in accordance with the intended use. The 2 mg presentation of alteplase is not indicated 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 are indicated for use in these indications.

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

When ACTILYSE is being considered for the treatment of acute massive pulmonary embolism, the diagnosis should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning. There is no data regarding positive effects on mortality and late morbidity when a thrombolytic agent is used to treat acute massive pulmonary embolism.

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.

Hypersensitivity

Immune-mediated hypersensitivity reactions associated with the administration of ACTILYSE can be caused by the active substance alteplase, gentamicin (a trace residue from the manufacturing process), any of the excipients (see also section 4.3) or the stopper of the glass vials (ACTILYSE powder and sterile water for injection) which contains natural rubber (a derivative of latex).

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). 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.

Bleeding
The most common complication encountered during ACTILYSE therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during ACTILYSE therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all possible bleeding sites (including those following catheter insertion, arterial and venous puncture cutdown and needle puncture). The use of rigid catheters, intramuscular injections and non-essential handling of the patient should be avoided during treatment with ACTILYSE.

Should serious bleeding occur, in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued and concomitant heparin administration should be terminated immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents should also be considered.

A dose exceeding 100 mg of ACTILYSE should not be given in acute myocardial infarction as well as acute massive pulmonary embolism and 90 mg in acute ischaemic stroke because it has been associated with an increase in intracranial bleeding.

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:

- recent intramuscular injection or small recent traumas, such as biopsies, puncture of major vessels, cardiac massage for resuscitation
- conditions with an increased risk of haemorrhage, which are not mentioned under contraindications
- patients receiving oral anticoagulant 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.

For the treatment of acute myocardial infarction and acute massive pulmonary embolism the following special warnings and precautions apply in addition:

- systolic blood pressure > 160 mmHg, see also section 4.3
- advanced age, which may increase the risk of intracerebral haemorrhage. As the therapeutic benefit is also positive in elderly patients, the risk-benefit-evaluation should be carried out carefully.

For the treatment of acute myocardial infarction the following special warnings and precautions apply in addition:

Arrhythmias
Coronary thrombolysis may result in arrhythmia associated with reperfusion. Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

Glyco-Protein IIb/IIIa antagonists
The concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

Thrombo-embolism
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.

For the treatment of acute ischaemic stroke the following special warnings and precautions apply in addition:
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, Acute Ischaemic Stroke).

Bleeding
Intracerebral haemorrhages represent the major adverse event (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:

- all situations listed in section Contraindications and in general all situations involving a high risk of haemorrhage
- late time-to-treatment onset
- patients pre-treated with acetylsalicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if ACTILYSE treatment is delayed.
- compared to younger patients, patients of advanced age (over 80 years) may have a somewhat poorer outcome independent of treatment and may have an increased risk of intracerebral haemorrhage when thrombolysed. In general, the benefit-risk of thrombolysis in patients of advanced age remains positive. Thrombolysis in AIS patients should be evaluated on individual benefit-risk basis.

Treatment must not be initiated later than 4.5 hours after the onset of symptoms because of unfavourable benefit/risk ratio mainly based on the following:

- positive treatment effects decrease over time
- particularly in patients with prior ASA treatment the mortality rate increases
- increased risk of symptomatic haemorrhage.

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

Special patient groups at reduced benefit-risk
The therapeutic benefit is reduced in patients who have had a prior stroke (see also section 4.3) or in whom uncontrolled diabetes exists. The benefit/risk ratio is considered less favourable, although still positive in these patients.

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 of treatment.

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

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

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies with ACTILYSE and medicinal products commonly administered in patients with acute myocardial infarction have been performed.

Drugs affecting coagulation/platelet function
Medicinal products that affect coagulation or those that alter platelet function (e.g. coumarin derivatives, platelet aggregation inhibitors, heparin) may increase the risk of bleeding prior to, during or after ACTILYSE therapy, see section 4.3.

ACE inhibitors
Concomitant treatment with ACE inhibitors may enhance the risk of suffering a hypersensitivity reaction (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of ACTILYSE in pregnant women.

Non-clinical studies performed with alteplase in doses higher than human doses exhibited fetal immaturity and/or embryotoxicity, secondary to the known pharmacological activity of the drug. Alteplase is not considered to be teratogenic (see section 5.3).

In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk.

Breastfeeding
It is not known if alteplase is excreted into human milk.

Fertility
Clinical data on fertility are not available for ACTILYSE. Nonclinical studies performed with alteplase showed no adverse effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

a. 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) resulting 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.

The type of bleeds associated with thrombolytic therapy can be divided into two broad categories:
- superficial bleeding, normally from punctures or damaged blood vessels,
- internal bleeding at any site or body cavity.

With intracranial haemorrhage neurological symptoms such as somnolence, aphasia, hemiparesis, convulsion may be associated.

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 very small in comparison to the number in the trial for acute myocardial infarction. Therefore, small numerical differences observed in comparison with the number of acute myocardial infarction were presumably attributable to the small sample size. Except for intracranial haemorrhage as side effect in the indication acute

ischaemic stroke and reperfusion arrhythmias in the indication acute myocardial infarction there is no medical reason to assume that the qualitative and quantitative side effect profile of ACTILYSE in the indications acute massive pulmonary embolism and acute ischaemic stroke is different from the profile in the indication acute myocardial infarction.

b. Tabulated summary of adverse reactions

Adverse reactions in myocardial infarction, pulmonary embolism and ischaemic stroke

System Organ Class	**Adverse Reaction**
Immune system disorders	
rare	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
Eye disorders	
rare	eye haemorrhage
Cardiac disorders	
rare	pericardial haemorrhage
Vascular disorders	
very common	haemorrhage, such as haematoma
rare	embolism[#], which may lead to corresponding consequences in the organs concerned
not known*	bleeding of parenchymatous organs such as hepatic haemorrhage*
Respiratory, thoracic and mediastinal disorders	
common	respiratory tract haemorrhage, such as - pharyngeal haemorrhage
uncommon	- haemoptysis - epistaxis
rare	- pulmonary haemorrhage
Gastrointestinal disorders	
common	gastrointestinal haemorrhage such as - gastric haemorrhage - gastric ulcer haemorrhage - rectal haemorrhage - haematemesis - melaena - mouth haemorrhage - gingival bleeding
rare	retroperitoneal haemorrhage, such as retroperitoneal haematoma nausea
not known*	vomiting* Nausea and vomiting can also occur as symptoms of myocardial infarction
Skin and subcutaneous tissue disorders	
common	ecchymosis

System Organ Class	Adverse Reaction
Renal and urinary disorders	
common	urogenital haemorrhage such as - haematuria - haemorrhage urinary tract
General disorders and administration site conditions	
common	injection site haemorrhage, puncture site haemorrhage such as - catheter site haematoma - catheter site haemorrhage
Investigations	
uncommon	blood pressure decreased
not known*	body temperature increased*
Injury and poisoning and procedural complications	
not known*	fat embolism*, which may lead to corresponding consequences in the organs concerned
Surgical and medical procedures	
not known*	transfusion*
Nervous system disorders	
very common (ischaemic stroke)	intracranial haemorrhage such as - cerebral haemorrhage - cerebral haematoma - haemorrhagic stroke - haemorrhagic transformation of stroke - intracranial haematoma - subarachnoid haemorrhage
common (myocardial infarction & pulmonary embolism)	intracranial haemorrhage such as - cerebral haemorrhage - cerebral haematoma - haemorrhagic stroke - haemorrhagic transformation of stroke - intracranial haematoma - subarachnoid haemorrhage
Cardiac disorders	
uncommon (myocardial infarction)	reperfusion arrhythmias[#], such as - arrhythmia - extrasystoles - atrial fibrillation - atrioventricular block first degree to atrioventricular block complete - bradycardia - tachycardia - ventricular arrhythmia - ventricular fibrillation - ventricular tachycardia

* This adverse reaction has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than “rare”, but might be lower. A precise frequency estimation is not possible as the adverse drug reaction did not occur in a clinical trial database of 8299 patients.

[#] BI frequency of these acknowledged adverse reactions was based on data from the clinical trial (ASSENT II).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

Symptoms
If the maximum recommended dose is exceeded the risk of intracranial bleeding increases. Notwithstanding the relative fibrin specificity of ACTILYSE, a clinically significant reduction in fibrinogen and other blood coagulation components may occur after overdosage.

Therapy
In most cases, it is sufficient to await the physiological regeneration of these factors, after the ACTILYSE therapy has been terminated. If, however, severe bleeding results, the infusion of fresh frozen plasma or fresh blood is recommended and if necessary synthetic antifibrinolytics may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, ATC code: B01AD02

Mechanism of action
The active ingredient of ACTILYSE is alteplase, a recombinant human tissue-type plasminogen activator, a glycoprotein, which activates plasminogen directly to plasmin. When administered intravenously, alteplase remains relatively inactive in the circulatory system. Once bound to fibrin, it is activated, inducing the conversion of plasminogen to plasmin leading to the dissolution of the fibrin clot.

Pharmacodynamic effects
Due to its relative fibrin-specificity, alteplase at a dose of 100 mg leads to a modest decrease of the circulating fibrinogen levels to about 60% at 4 hours, which is generally reverted to more than 80% after 24 hours. Plasminogen and alpha-2-antiplasmin decrease to about 20% and 35% respectively after 4 hours and increase again to more than 80% at 24 hours. A marked and prolonged decrease of the circulating fibrinogen level is only seen in few patients.

Clinical efficacy and safety

Acute Myocardial Infarction (AMI) patients
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. Administration of 100 mg ACTILYSE over 90 minutes, with concomitant intravenous heparin infusion, led to a lower mortality after 30 days (6.3%) as compared to the administration of streptokinase, 1.5 million IU over 60 minutes, with subcutaneous or intravenous heparin (7.3%). The 1% absolute decrease in 30-day mortality for ACTILYSE compared to streptokinase was statistically significant ($p = 0.007$). ACTILYSE-treated patients showed higher infarct related vessel patency rates at 60 and 90 minutes after thrombolysis than the streptokinase-treated patients. No differences in patency rates were noted at 180 minutes or longer.

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%, $p = 0.0003$). The reduction of the risk of

bleeding is likely to be related to the increased fibrin specificity of tenecteplase and to its weight adapted regimen.

3-hour infusion in AMI patients
In a double-blind, randomised trial (5013 patients) comparing ACTILYSE to placebo (ASSET study) patients infused with ACTILYSE within 5 hours of the onset of symptoms of acute myocardial infarction experienced improved 30-day survival compared to those treated with placebo. At 1 month, the overall mortality rates were 7.2% for the ACTILYSE-treated group and 9.8% for the placebo-treated group ($p = 0.001$). This benefit was maintained at 6 months for ACTILYSE-treated patients (10.4%) compared to those treated with placebo (13.1%, $p = 0.008$).

In a double-blind, randomised trial (721 patients) comparing ACTILYSE to placebo, patients infused with ACTILYSE 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 ACTILYSE had a 19% reduction in infarct size, as measured by cumulative release of HBD (α-hydroxybutyrate dehydrogenase) activity compared to placebo-treated patients ($p = 0.001$). Patients treated with ACTILYSE 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 ACTILYSE-treated patients was reduced to 3.7% compared to 6.3% in placebo-treated patients (1-sided $p = 0.05$). 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 placebo controlled trial (LATE) in 5711 AMI patients with onset of symptoms between 6 and 24 hours a 100 mg ACTILYSE over 3 hours infusion was compared with placebo. A non-significant reduction of 14.1% (95% CI 0 - 28.1%, $p > 0.05$) in 30-day-mortality was observed with ACTILYSE. In a pre-specified survival analysis in patients treated within 12 hours of symptom onset, a significant 25.6% reduction in mortality in favour of ACTILYSE (95% CI 6.3 - 45%; $p = 0.023$) was observed.

<u>Acute Massive Pulmonary Embolism patients</u>
In a comparative randomised trial of alteplase versus urokinase in 63 patients with angiographically documented acute massive pulmonary embolism both treatment groups experienced a significant reduction in pulmonary embolism-induced pulmonary hypertension. Pulmonary haemodynamics improved significantly faster with ACTILYSE than with urokinase.

<u>Acute Ischaemic Stroke patients</u>
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. Thrombolysis in AIS patients should be evaluated on individual benefit-risk basis.

Two placebo-controlled, double-blind trials (NINDS t-PA Stroke Trial, Part 1 and Part 2) enrolled patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computerized tomography (CT) scan was performed prior to treatment to rule out the presence of symptomatic intracranial haemorrhage (SICH). 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 or > 400 mg/dL. Patients were randomised to receive either 0.9 mg/kg ACTILYSE (maximum of 90 mg), or placebo. ACTILYSE 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) 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 suggested improved 3-months outcome associated with ACTILYSE treatment using the following stroke assessment scales: Barthel Index, Modified Rankin Scale (mRS), Glasgow Outcome Scale, and the

NIHSS. A second study (NINDS-Part 2, n = 333) assessed clinical outcome at 3 months as the primary outcome. A favourable outcome was 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 odds ratio for favourable outcome in the ACTILYSE 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 ACTILYSE on other neurologic and disability scales. 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-months outcome treatment effects observed in the Part 1 study. The incidences of all-cause 90-day mortality, SICH, and new ischaemic stroke following ACTILYSE treatment compared to placebo indicated a significant increase in symptomatic SICH (according to NINDS definition) following ACTILYSE treatment within 36 hours (ACTILYSE 6.4%; Placebo 0.65%). In ACTILYSE-treated patients, there were no increases compared to placebo in the incidences of 90-day mortality or severe disability (ACTILYSE 20.5%; Placebo 17.3%).

A pooled analysis of 2775 patients from 6 major randomised clinical trials (NINDS part 1 and 2, two ECASS trial and ATLANTIS part A and B) evaluated the disability status of patients treated with ACTILYSE or placebo. In this analysis, the odds of a favourable outcome at 3 months increased as the time to treatment with ACTILYSE decreased. A SICH rate was seen in 5.9% of patients treated with ACTILYSE versus 1.1% of controls ($p < 0.0001$) which was associated with age but not with time to treatment. This analysis strongly confirms that rapid treatment with ACTILYSE is associated with better outcomes at 3 months. It also provides evidence that the therapeutic window may extend as far out as 4.5 hours.

In a large observational study (SITS-MOST: The Safe Implementation of Thrombolysis in Stroke-Monitoring Study) the safety and efficacy of ACTILYSE for acute stroke treatment within 3 hours in a routine clinical setting was assessed and compared with results from randomised clinical trials (RCTs). All patients had to be compliant with the European summary of the product characteristics of ACTILYSE. Treatment and outcome data of 6483 patients from 285 centres in 14 European countries were collected. Primary outcome were symptomatic intracranial haemorrhage within 24 hours and mortality at 3 months. The rate of SICH found in SITS-MOST was comparable with the SICH rate as reported in randomised trials 7.3% (95% CI 6.7 - 8.0) in SITS-MOST versus 8.6% (95% CI 6.1 - 11.1) in RCTs. Mortality was 11.3% (95% CI 10.5 - 12.1) in SITS-MOST versus 17% (95% CI 13.9 - 20.7) in RCTs. The results of SITS-MOST indicate that, the routine clinical use of ACTILYSE within 3 hours of stroke onset is as safe as reported in randomised clinical trials.

The ECASS III trial as 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 European summary of product characteristics (SmPC) except the time-window. After exclusion of brain haemorrhage or major infarction by computed tomography, patients with acute ischaemic stroke were randomised in a 1:1 double-blind fashion to intravenous alteplase (0.9 mg/kg bodyweight) or placebo. The primary end point was disability at 90 days, dichotomized for favourable (modified Rankin scale [mRS] 0 to 1) or unfavourable (mRS 2 to 6) outcome. The principal secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included mortality, SICH, and serious adverse events. A total of 821 patients were (418 alteplase/403 placebo) randomised. More patients achieved favourable outcome with alteplase (52.4%) versus placebo (45.2%; odds ratio [OR], 1.34; 95% CI 1.02 - 1.76; $p = 0.038$). On the global analysis, outcome was also improved (OR, 1.28; 95% CI 1.00 - 1.65; $p = 0.048$). The incidence of any ICH/SICH was higher with alteplase versus placebo (any ICH 27.0% versus 17.6%, $p = 0.0012$; SICH by NINDS definition 7.9% versus 3.5%, $p = 0.006$; SICH by ECASS III definition 2.4% versus 0.2%, $p = 0.008$). Mortality was low and not significantly different between alteplase (7.7%) and placebo (8.4%; $p = 0.681$). The results of ECASS III show that ACTILYSE between 3 and 4.5 hours after symptom onset significantly improves clinical outcomes in patients with acute ischaemic stroke.

The safety and efficacy of ACTILYSE for acute ischaemic stroke treatment up to 4.5 hours time onset to treatment (OTT) has been assessed by an ongoing AIS registry (SITS-ISTR:

The Safe Implementation of Thrombolysis in Stroke registry). Primary outcome and mortality data of 21,566 patients in the 0 to 3 hours time window were compared with data from 2,376 patients treated between 3 to 4.5 hours after onset of AIS (data from 2010). The incidence of symptomatic intracerebral haemorrhage (according to the NINDS definition) was found to be slightly higher in the 3 to 4.5 hours time window (7.4%) as compared with the up to 3 hours time window (7.1%; adjusted odds ratio 95% CI: 1.18 (0.99-1.41) p=0.06). Mortality rates at 3 months were similar for the 3 to 4.5 hours time window (12.0%) with the 0 to 3 hours time window 12.3%.

5.2 Pharmacokinetic properties

Alteplase is cleared rapidly from circulating blood. The organ primarily responsible for clearance is the liver (plasma clearance 550-680 mL/min). The level of alteplase present in plasma falls to 50% of the initial level within 5 minutes, to approximately 20% after 10 minutes and to less than 10% after 20 minutes (plasma half-life $t_{1/2\ \alpha}$ is 4 – 5 min). For the residual amount remaining in a deep compartment, a β half-life of about 40 minutes has been measured.

5.3 Preclinical safety data

In subchronic toxicity studies in rats and marmosets no other unexpected side effects than increased bleeding tendency at higher doses were found. No indications of a mutagenic potential were found in mutagenic tests.

In pregnant animals no teratogenic effects were observed after intravenous infusion of pharmacologically effective doses. In rabbits embryotoxicity (embryolethality, growth retardation) was induced by more than 3 mg/kg/day. No effects on peri-postnatal development or on fertility parameters were observed in rats with doses up to 10 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

arginine
nitrogen
phosphoric acid
polysorbate 80
water for injection

6.2 Incompatibilities

The reconstituted solution may be diluted further with sterile physiological saline solution (0.9%) up to a minimal concentration of 0.2 mg alteplase per mL.

Further dilution with sterilised water for injections or the use of carbohydrate solutions is not recommended due to increasing formation of turbidity of the reconstituted solution.

ACTILYSE should not be mixed with other medicinal products in the same infusion vial nor the same intravenous line (not even with heparin) (see section 4.2).

6.3 Shelf life

36 months

Chemical and physical in-use stability
The reconstituted solution has been demonstrated to be stable for 24 hours at 2 - 8°C and for 8 hours at 25ºC.

Microbiological in-use stability
From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage

Protect from light.
Store below 25ºC.

6.5 Nature and contents of container

Individual packs of ACTILYSE 10 mg injection vial and 10 mL water for injection, ACTILYSE 20 mg injection vial and 20 mL water for injection (not marketed), and ACTILYSE 50 mg injection vial and 50 mL water for injection.

6.6 Special precautions for disposal and other handling of the product

For reconstitution to a final concentration of 1 mg alteplase per mL the full volume of solvent provided should be transferred to the vial containing the ACTILYSE powder. For this purpose a transfer cannula is included with the 20 mg and 50 mg presentations, which is to be used. For the 10 mg presentation a syringe should be used.

Under aseptic conditions the contents of an injection vial of ACTILYSE (10 mg, 20 mg or 50 mg) 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

The reconstituted solution is a clear and colourless to pale yellow solution. Prior to administration it should be inspected visually for particles and colour. The 1 mg/mL reconstituted solution may be diluted further with sterile sodium chloride 9 mg/mL (0.9%) solution for injection up to a minimal concentration of 0.2 mg/mL since the occurrence of turbidity of the reconstituted solution cannot be excluded.

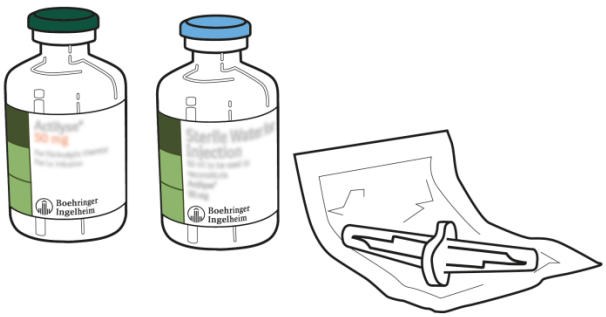
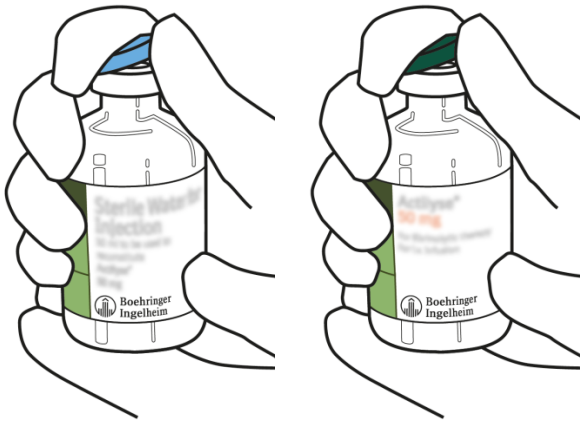
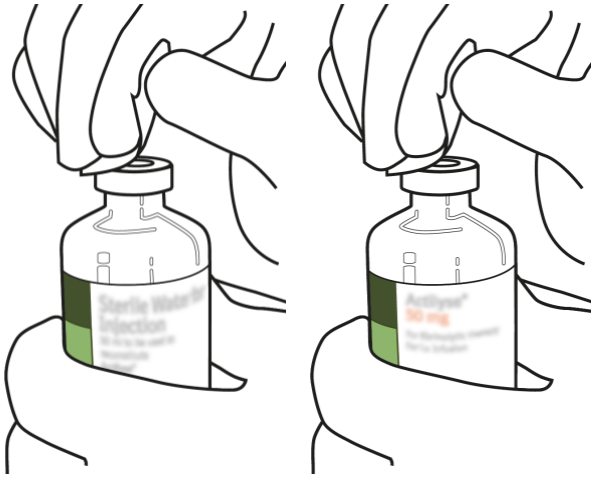
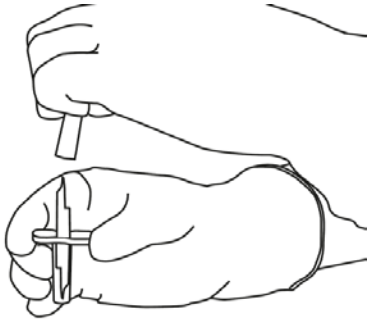
A further dilution of the 1 mg/mL reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not recommended due to increasing formation of turbidity of the reconstituted solution.

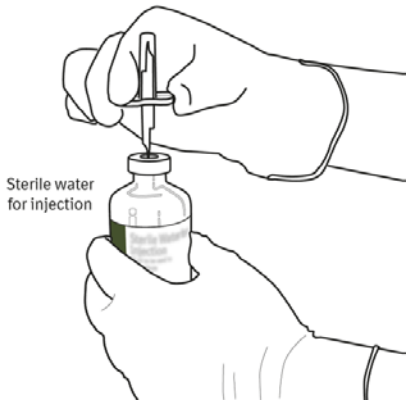
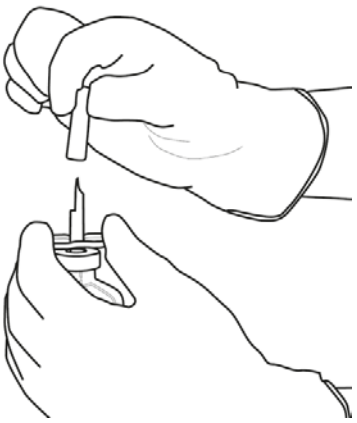
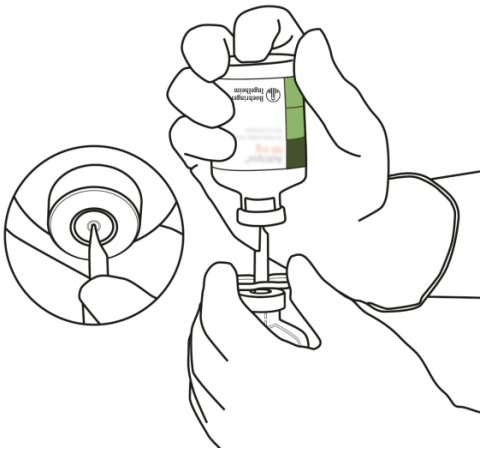
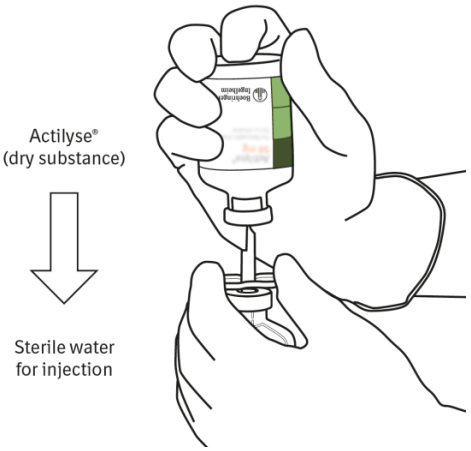
ACTILYSE should not be mixed with other drugs, neither in the same infusion-vial nor the same venous line (not even with heparin).

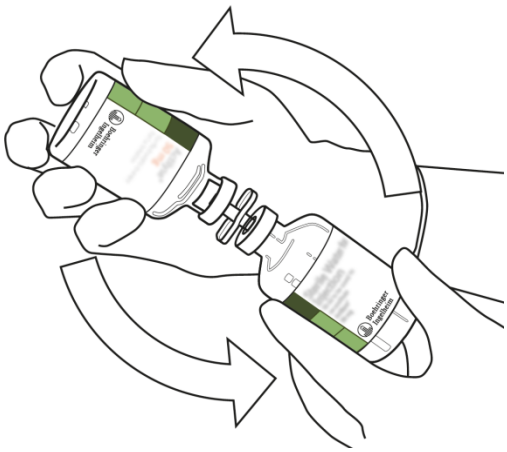
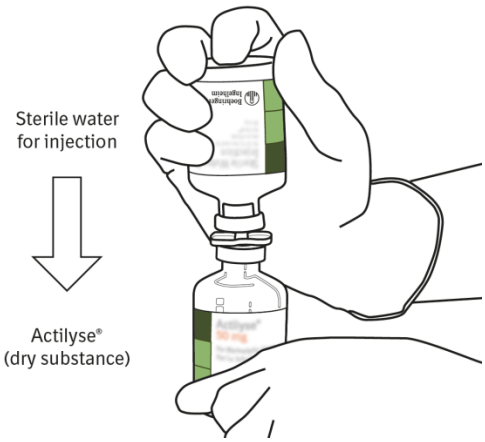
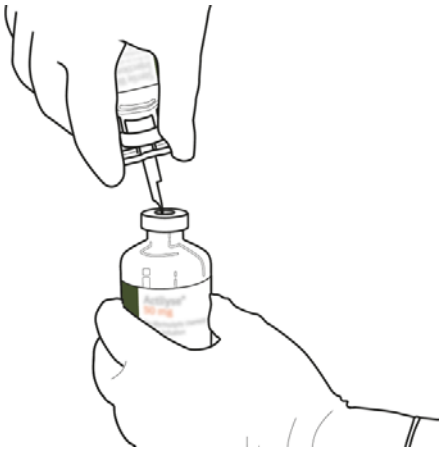
For incompatibilities see section 6.2.

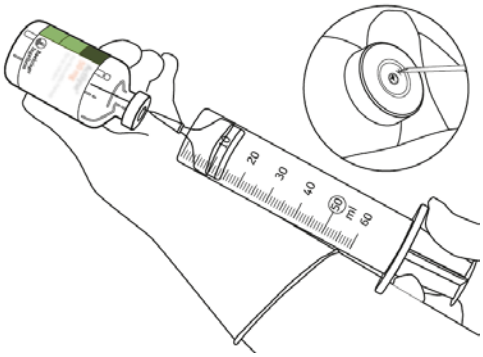
The reconstituted solution is for single use only. Any unused solution or waste material should be disposed in accordance with the local requirements.

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 center with the transfer cannula, by pressing gently but firmly, without twisting.	
6	Hold the sterile water vial and the transfer cannula steady with one hand using the two side flaps. Remove the remaining cap on top of the transfer cannula.	
7	Hold the sterile water vial and the transfer cannula steady with one hand using the two side flaps. Hold the vial with ACTILYSE dry substance 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 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 using a needle and a syringe. Do not use the puncture location from the transfer cannula to avoid leakage.	
13	Use immediately. Dispose of any unused solution.	

(*if a transfer cannula is included in the kit. The reconstitution can also be performed with a syringe and a needle.)

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
P O Box 76-216
Manukau City
Auckland
NEW ZEALAND

Telephone: 0800 802 461
Facsimile: 0508 774 748

9. DATE OF FIRST APPROVAL

19 March 1987

10. DATE OF REVISION OF THE TEXT

14 February 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Editorial changes to improve clarity of dosing instructions for acute ischaemic stroke.
4.3	Reinstatement of contraindication.
4.4	- *Traceability*: Addition of traceability statement relevant for biological medicinal products. - *Hypersensitivity*: Deletion of duplicated information and alignment of wording with EU SmPC
4.5	Editorial changes to avoid repetition of information on ACE inhibitors already presented in Section 4.4
5.1	*Clinical efficacy and safety*: Editorial changes to update numbers from the SITS-ISTR registry
8	Sponsor telephone and facsimile numbers updated