AUSTRALIAN PRODUCT INFORMATION – ACTILYSE® CATHFLO® (alteplase) powder for injection

1 NAME OF THE MEDICINE

alteplase (rch)

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION and PHARMACEUTICAL FORM

ACTILYSE CATHFLO is presented as a sterile, white to off-white, lyophilised powder, intended for intra-catheter instillation into dysfunctional central venous access devices, including those used for haemodialysis, after reconstitution with sterile Water for Injections.

ACTILYSE CATHFLO is available in boxes containing either:

- 1 vial of ACTILYSE CATHFLO 2 mg alteplase (corresponding to 1,160,000 IU) in up to 93.3 mg dry powder; or
- 5 vials of ACTILYSE CATHFLO 2 mg alteplase (corresponding to 1,160,000 IU) in up to 93.3 mg dry powder.

The specific activity of alteplase in-house reference material is 580,000 IU/mg. This has been confirmed by comparison with the second international WHO standard for t-PA. The specification for the specific activity of alteplase is 522,000 to 696,000 IU/mg.

For the full list of excipients, see Section 6.1 List of excipients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACTILYSE CATHFLO is indicated for the thrombolytic treatment of occluded central venous access devices including those used for haemodialysis.

The 2 mg strength of alteplase (ACTILYSE CATHFLO) is the only recommended presentation for use in this indication.

See also section 4.4 Special Warnings and Precautions for use ─ Paediatric Use.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

For the thrombolytic treatment of occluded central venous access devices including those used for haemodialysis, a dose of up to 2 mg of ACTILYSE CATHFLO instilled up to two times for each occlusion, can be used to restore function of ports, single and multiple lumen catheters including those used for haemodialysis, which became dysfunctional due to thrombotic occlusion.

In patients with a body weight of 30 kg or more, a total dose of 2 mg alteplase in 2 mL should be instilled into the occluded central venous access device.

In patients with a body weight below 30 kg, the volume of reconstituted solution to be instilled into the occluded central venous access devices should correspond to 110% of the internal lumen volume of the device. The total dose must not exceed 2 mg.

Re-administration

If occluded central venous access device functionality is not restored at 120 minutes after the first dose, a second dose of equal amount may be instilled.

There is no efficacy or safety information on dosing in excess of 2 mg per dose for this indication. Studies have not been performed with administration of total doses greater than 4 mg (two x 2 mg doses).

Method of Administration

The reconstituted solution is instilled into the lumen of the occluded central venous access device and is for immediate use.

Instructions for Reconstitution

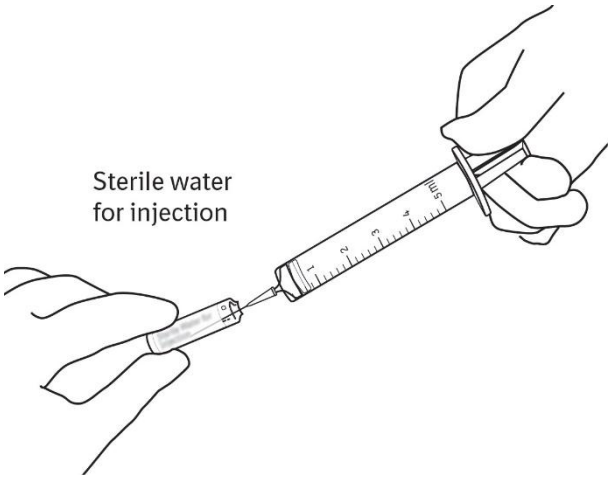
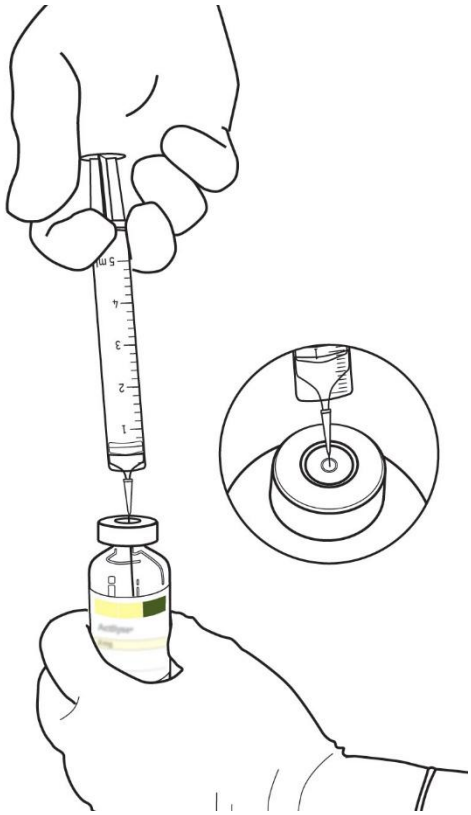
Do not use vial if vacuum is not present.

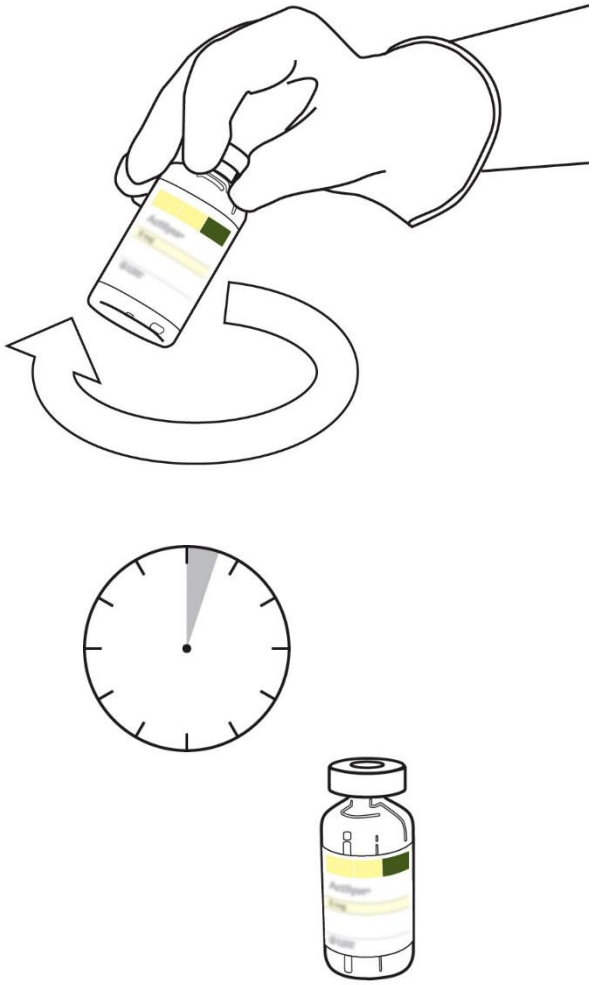
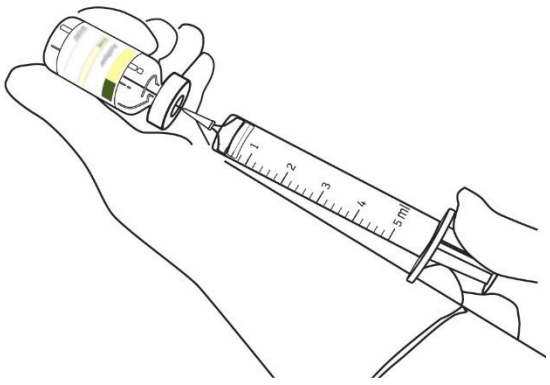
ACTILYSE CATHFLO should be reconstituted to a final concentration of 1 mg alteplase per mL by aseptically adding 2.2 mL of sterile Water for Injection into the ACTILYSE CATHFLO dry powder vial (the total amount of powder in the vial includes an overage which will remain in the vial/transfer syringe so that the amount practically administered will be 2 mg alteplase). For this purpose, a syringe with a suitable measuring precision should be used.

Reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterile Water for Injection into the lyophilised cake.

It is important that ACTILYSE CATHFLO be reconstituted only with sterile Water for Injection without preservatives. Do not use bacteriostatic Water for Injection.

Instructions for reconstituting ACTILYSE CATHFLO		
1	Reconstitute immediately before administration.	
2	Remove the protective cap on the vial containing ACTILYSE CATHFLO dry substance by flipping it up with a thumb.	
3	Swab the rubber top of the vial with an alcohol wipe.	

4	Aseptically withdraw 2.2 mL sterilised Water for Injection.	
5	Transfer the 2.2 mL sterilised Water for Injection into the ACTILYSE CATHFLO vial by introducing the needle vertically into the middle of the rubber stopper, directing the diluent stream into the powder.	

6	Take the vial with reconstituted ACTILYSE CATHFLO 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.	
7	The reconstituted solution consists of 1 mg/mL ACTILYSE CATHFLO. It should be clear and colourless to pale yellow and it should not contain any particles.	
8	Remove the amount required using a needle and a syringe.	
9	Use immediately. Dispose of any unused solution.	

The reconstituted lyophilised preparation results in a colourless to pale yellow transparent solution containing ACTILYSE CATHFLO 1 mg per mL at a pH of 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

ACTILYSE CATHFLO should not be mixed with other drugs, neither in the same injection vial nor within the catheter lumen. Prior to instillation, the 1 mg/mL reconstituted solution should be visually inspected for particles and colour.

Instructions for Dilution

The reconstituted solution (1 mg alteplase per mL) may be diluted further, immediately before instillation, with sterile physiological saline solution (0.9% Sodium Chloride for Injection) up to a minimal concentration of 0.2 mg alteplase per mL. Further dilution of the reconstituted solution with sterile physiological saline solution (0.9% Sodium Chloride for Injection) below a minimal concentration of 0.2 mg alteplase per mL is not recommended since the occurrence of turbidity of the reconstituted solution cannot be excluded.

A further dilution of the 1 mg/mL reconstituted solution with sterile Water for Injection, 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 CATHFLO solution. Because ACTILYSE CATHFLO contains no preservatives, it should be reconstituted immediately before use.

Instructions for Instillation of the ACTILYSE CATHFLO Solution into the Catheter

1. Reconstitute the contents of the ACTILYSE CATHFLO 2 mg injection vial to the final concentration of 1 mg alteplase per mL (see Instructions for Reconstitution subsection above). For catheters with a lumen volume greater than 2 mL, ACTILYSE CATHFLO can be further diluted with sterile physiological saline solution (0.9% Sodium Chloride for Injection) to the desired volume (see Instructions for Dilution subsection above).

2. Instil the appropriate dose of ACTILYSE CATHFLO into the occluded central venous access device.

3. After 30 minutes of dwell time, assess catheter functionality by attempting to aspirate blood.

   If the catheter is functional, go to Step 6.
   If the catheter is not functional, go to Step 4.

4. After 120 minutes of dwell time, assess catheter functionality by attempting to aspirate blood and catheter contents.

   If the catheter is functional, go to Step 6.
   If the catheter is not functional, go to Step 5.

5. If catheter functionality is not restored at 120 minutes of dwell time after the first dose, a second dose of equal amount may be instilled. Repeat the procedure beginning with Step 1. If after a second dose of ACTILYSE CATHFLO the catheter functionality has not been restored, consider the need for catheter replacement.

6. If catheter functionality has been restored, aspirate 4-5 mL of blood in patients with a body weight of 10 kg or more, or 3 mL in patient with a body weight of less than 10 kg, to remove ACTILYSE CATHFLO and residual clot, and gently irrigate the catheter with sterile physiological saline solution (0.9% Sodium Chloride for Injection).

4.3 CONTRAINDICATIONS

ACTILYSE CATHFLO should not be instilled into the occluded central venous access device of patients with known hypersensitivity to alteplase or any of the excipients (listed under 6.1 List of Excipients).

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 (ACTILYSE CATHFLO) is not indicated for use

in acute myocardial infarction, acute pulmonary embolism or acute ischaemic stroke (due to risk of massive under dosing). Only 10, 20 and 50 mg vials are indicated for use in those indications.

For the treatment of occluded central venous access devices including those used for haemodialysis:

Co-instillation of heparin

The co-instillation of heparin with ACTILYSE CATHFLO has not been shown to improve the rates of catheter function restoration and is not recommended. If heparin is considered necessary to prevent re-occlusion, this should be instilled separately after catheter function has been restored.

Damage to the vascular wall and collapse of catheters

Catheter dysfunction may be caused by a variety of conditions other than thrombus formation, such as catheter malposition, mechanical failure, constriction by a suture, and lipid deposits or drug precipitates within the catheter lumen. Because of the risk of damage to the vascular wall or collapse of soft-walled catheters, vigorous suction must not be applied during attempts to determine catheter occlusion. Excessive pressure must be avoided when ACTILYSE CATHFLO is instilled into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the circulation.

Bleeding

The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. ACTILYSE CATHFLO has not been studied in patients with occluded catheters known to be at risk for bleeding events that may be associated with the use of thrombolytics.

Caution should be exercised with patients:

- who have active internal bleeding;
- who have had any of the following within 48 hours before the start of the instillation: surgery, obstetrical delivery, percutaneous biopsy of viscera or deep tissues, or puncture of non-compressible vessels;
- who have thrombocytopenia other haemostatic defects (including those secondary to severe hepatic or renal disease);
- who have any condition for which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location; or
- who are at high risk of embolic complications (e.g. venous thrombosis in the region of the catheter).

Death and permanent disability have been reported in patients who have experienced stroke and other serious bleeding episodes when receiving pharmacologic doses of a thrombolytic. Should serious bleeding in a critical location (e.g. intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with ACTILYSE CATHFLO should be stopped and the drug should be withdrawn from the catheter.

Infection

ACTILYSE CATHFLO should be used with caution in the presence of known or suspected infection in the catheter. Using ACTILYSE CATHFLO in patients whose catheters are occluded by infected thrombi may release micro-organisms into the systemic circulation leading to sepsis. As with all catheterisation procedures, care should be taken to maintain aseptic technique and appropriate antibiotic treatment used as necessary.

Re-administration

Patients may receive up to 2 mg of ACTILYSE CATHFLO instilled up to two times for each occlusion (see Section 4.2 Dose and Method of Administration). In the event of continuing catheter dysfunction, other causes for dysfunction should be sought. Subsequent occlusions may be treated similarly although it should be noted that frequent re-occlusions may indicate the need for catheter replacement.

Hypersensitivity

Although physiologically relevant plasma concentrations are not reached, hypersensitivity might occur. Hypersensitivity reactions associated with the instillation of ACTILYSE CATHFLO can be caused by the active substance alteplase or any of the excipients (see Section 4.3 Contraindications). If a severe

hypersensitivity reaction occurs, the instillation should be discontinued and appropriate treatment should be promptly initiated.

Antibody formation in patients receiving one or more doses of alteplase for restoration of occluded central venous access devices has not been studied.

Traceability

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

Use in the Elderly

In 312 patients enrolled in the clinical trials who were age 65 years and over, no incidents of intracranial haemorrhage, embolic events, or major bleeding events were observed. 103 of these patients were age 75 years and over, and 12 were age 85 years and over. The effect of ACTILYSE CATHFLO on common age-related co-morbidities has not been studied. In general, caution should be used in elderly patients with conditions known to increase the risk of bleeding (see Section 4.4 Special Warnings and Precautions for Use ─ Bleeding).

Paediatric Use

There is insufficient data to establish the safety and efficacy of ACTILYSE CATHFLO in preterm neonates. The use of ACTILYSE CATHFLO in preterm neonates is not recommended.

Effect on Laboratory Tests

Potential interactions between ACTILYSE CATHFLO and laboratory tests have not been studied.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs affecting coagulation/platelet function

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

ACE inhibitors

Concomitant treatment with Angiotensin Converting Enzymes (ACE) inhibitors may enhance the risk of suffering a hypersensitivity reaction (see Section 4.8 Adverse Effects (Undesirable Effects)). Monitoring is recommended particularly for patients receiving concomitant ACE inhibitors.

Other medicines

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

Use in Pregnancy (Category B1)

Studies have shown that ACTILYSE CATHFLO 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 CATHFLO should be given to pregnant women only if the need clearly outweighs the potential risk.

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

Use in Lactation

It is not known whether ACTILYSE CATHFLO is excreted in human milk. Because many drugs are excreted by this route, caution should be exercised when ACTILYSE CATHFLO is administered to breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of the safety profile

Under systemic application of alteplase with a considerably higher therapeutic dose range, bleeding at any site or body cavity have been observed; however, in clinical trials investigating ACTILYSE CATHFLO at a dose of 2 mg in catheter clearance indication, currently only gastrointestinal bleeding, nose bleeds and vascular puncture site bleedings were observed.

Because the clinical trials performed with ACTILYSE CATHFLO are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials cannot be directly compared to each other. The rate observed in clinical trials might not reflect the rates observed in practice.

In clinical trials investigating treatment of occluded catheters with ACTILYSE CATHFLO (with a total exposure of 1432 patients treated with at least one dose of alteplase), the following adverse reactions were observed:

Infections and infestations:

>0.1% and ≤ 1%: sepsis – In the clinical trial programme, six cases of catheter-related sepsis occurred in the range of 15 minutes up to 44 hours after application of ACTILYSE CATHFLO.

Gastrointestinal disorders:

>0.1% and ≤ 1%: gastrointestinal bleeding

General disorders and administration site conditions:

>0.1% and ≤ 1%: catheter related complications – In the clinical trial programme, catheter-related complications such as catheter lumen burst, injection site haemorrhage and thrombosis of vessels used for catheter placement were observed. These events might also be related to the underlying conditions of e.g. catheter placement.

>0.01% and ≤ 0.1%: fever

In total, three patients (0.2% of all treated patients) discontinued from the clinical trials due to serious adverse events. Two cases experienced sepsis and one case of catheter rupture occurred.

No reports of intracranial haemorrhage were found and no cases of thromboembolism were observed in clinical trials investigating treatment of occluded catheters with ACTILYSE CATHFLO. Non-serious and localised adverse events were not recorded in the clinical trials.

In literature reports of haemodialysis, no other adverse reactions were noted than those reported for other central venous devices.

However, in general all undesirable effects as found for the systemic application of alteplase may also occur during treatment of occluded catheters in cases where ACTILYSE CATHFLO (2 mg of alteplase) reaches the systemic circulation (e.g. haemorrhage, embolism, hypersensitivity, anaphylactoid

reactions, blood pressure decrease, nausea, vomiting, body temperature increased). However pharmacokinetic data indicate that physiologically relevant plasma concentrations are not reached using this dosage.

The most frequent adverse reaction associated with the systemic application of alteplase 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.

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).

Neurological symptoms such as somnolence, aphasia, hemiparesis and convulsion may be associated with intracranial haemorrhage.

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTILYSE CATHFLO therapy should be discontinued immediately and the drug should be withdrawn from the catheter.

The frequencies given below are based on adverse events reported for the systemic application of alteplase which may be causally related to alteplase treatment.

Cardiac disorders (related to the systemic application of alteplase in patients with myocardial infarction):

>10%: reperfusion arrhythmias (such as arrhythmia, extrasystoles, atrial fibrillation, atrioventricular block I° to complete, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with alteplase. 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 the systemic application of alteplase in patients with myocardial infarction or pulmonary embolism):

>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 the systemic application of alteplase in patients with acute ischaemic stroke):

>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)

The following adverse events related to the systemic application of alteplase in patients with myocardial infarction, pulmonary embolism or acute ischaemic stroke:

Gastrointestinal disorders:

>1% and ≤10%: gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, haemorrhage rectum, 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%: superficial bleeding, normally from punctures (injection site haemorrhage) or damaged blood vessels (such as catheter site haematoma, catheter site haemorrhage, puncture 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 allergic reactions. 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 alteplase are known. Transient antibody formation to alteplase 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 embolisation (cholesterol crystal embolisation), which may lead to corresponding consequences in the organs concerned

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

>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%: whole blood transfusion

Skin and subcutaneous tissue disorders:

>1% and ≤10%: ecchymosis

Vascular disorders:

>10%: haemorrhage (such as haematoma)

>0.1% and ≤1%: embolism (thrombotic embolisation), 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)

4.9 OVERDOSE

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

Should serious bleeding occur in a critical location (e.g. intracranial, gastrointestinal, retroperitoneal, pericardial), treatment with ACTILYSE CATHFLO should be stopped and the drug should be withdrawn from the catheter. Most patients can be managed by interruption of thrombolytic therapy, volume

replacement and manual pressure applied to the bleeding vessel if accessible. If necessary, blood loss and reversal of the bleeding tendency can be managed with fresh whole blood or packed red blood cells. In the event of clinically significant fibrinogen depletion, fresh frozen plasma or cryoprecipitate can be infused with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents may be used as a last option.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antithrombotic agents.

ATC code: B01AD02.

Mechanism of action

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

Instillation of ACTILYSE CATHFLO at a dose of 2 mg into the occluded catheter allows fibrinolysis to occur locally within the catheter and at the catheter tip without causing pharmacodynamic effects in the circulation.

Effect on Coagulation

ACTILYSE CATHFLO differs from other plasminogen activators in that it is fibrin-dependent. Relatively selective fibrinolysis with ACTILYSE CATHFLO, 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 co-precipitation of plasminogen within the fibrin clot. As a result, ACTILYSE CATHFLO produces clot dissolution *in vivo* with minimal systemic effects.

Clinical Trials

<u>Occluded central venous access devices including those used for haemodialysis</u>

Three clinical studies were performed in patients with improperly functioning central venous access devices.

A placebo-controlled, double-blind, randomised trial (Study A2055g) and a larger open-label trial (Study A2065g) investigated the use of alteplase in predominately adult patients who had an indwelling central venous access devices for administration of chemotherapy, total parenteral nutrition, or long-term administration of antibiotics or other medications.

Study A2055g investigated the efficacy of alteplase in restoring function to occluded central venous access devices in 150 patients with catheter occlusions up to 24 hours in duration. Patients were randomised to receive either alteplase 2 mg (or less for children who weighed below 30 kg, see section 4.2 Dose and Method of Administration) or placebo instilled into the lumen of the catheter. Catheter function was assessed at 120 minutes after instillation. All patients whose catheter function was not restored after 120 minutes of the initial dose were then administered up to two doses of alteplase. Intention-to-treat analysis shows that restoration of catheter function was achieved after administration of the first bolus in 74% (51/69) of patients randomised to alteplase and 17% (12/70) of patients randomised to placebo. The treatment difference was statistically significant ($p<0.0001$). In total, 90% (124/138) of all patients achieved restoration of catheter function after administration of up to two doses of alteplase.

Study A2065g was an open-label, single arm trial in 995 patients with catheter dysfunction and included patients with catheter occlusions present for any duration. Patients were treated with up to two doses alteplase 2 mg (or less for children who weighed below 30 kg, see section 4.2 Dose and Method of

Administration) instilled into the lumen of the catheter. Assessment for restoration of function was made at 30 minutes after each instillation. If function was not restored, catheter function was re-assessed at 120 minutes. In total, restoration of catheter function was achieved in 87% (844/968) of patients following administration of up to two doses of alteplase after a dwell time of 120 minutes. Successful restoration of catheter function was achieved in 52% (516/991) of patients and 77% (747/976) of patients following instillation of the first dose of alteplase after a dwell time of 30 minutes and 120 minutes, respectively. Of the 209 patients who received a second dose of alteplase, restoration of catheter function was achieved in 33% (70/209) of patients after a dwell time of 30 minutes and 46% (97/209) of patients after a dwell time of 120 minutes.

Across Studies A2505g and A2065g, 68% (796/1043) of patients with catheter occlusions present for less than 14 days had restored function after one dose, and 88% had function restored after up to two doses of alteplase. Of the 53 patients with catheter occlusions present for longer than 14 days, 57% of patients had function restored after a single dose, and 72% of patients had restored function after up to two doses of alteplase.

The third pivotal study (Study A2404g) was an open-label, single-arm trial in 310 children and adolescents between the ages of 2 weeks and 17 years who had catheter occlusions presented for any duration. Patients were treated with up to two doses of alteplase 2 mg instilled into the catheter lumen (or less for children who weighed below 30 kg, see section 4.2 Dose and Method of Administration). Restoration of function was assessed at 30 and 120 minutes (if required) after administration of each dose. The overall rate of catheter function was similar to that observed in Study A2065g. In total, restoration of catheter function was achieved in 75% (233/310) of patients following one dose of alteplase and 83% (257/310) of patients following two doses of alteplase, after a dwell time of 120 minutes respectively. Restored catheter function was achieved in 80% (44/55) of patients < 2 years of age and 83.5% (213/255) patients in those aged ≥ 2 years.

The three trials had similar rates of catheter function restoration among the catheter types studied (single-, double-, and triple-lumen, and implanted ports). No gender differences were observed in the rate of catheter function restoration. Results were similar across all age subgroups.

The use of alteplase for the restoration of patency of haemodialysis catheters were reported in the literature. Data from well-controlled clinical studies are limited. A systematic review of thrombolysis for the restoration of haemodialysis catheters (including four literature studies on the use of alteplase in a total of 154 occluded catheters) showed that the overall restoration rates of catheter functions ranged from 88% to 98% following treatments with alteplase. Haemodialysis patients with end-stage renal disease have also been studied in a variety of trials following the systematic review of thrombolysis for the restoration of haemodialysis catheters.

5.2 PHARMACOKINETIC PROPERTIES

Alteplase 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 alteplase 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.

When alteplase is instilled for restoration of occluded central venous access devices according to the instructions, circulating plasma levels of alteplase are not expected to reach pharmacologic concentrations. If a 2 mg dose of alteplase was administered by bolus injection directly into the systemic circulation (rather than instilled into the catheter), the concentration of circulating alteplase would be expected to return to undetectable limits within 30 minutes.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies with ACTILYSE CATHFLO have not been performed to determine mutagenesis.

Carcinogenicity

Studies with ACTILYSE CATHFLO have not been performed to determine carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are: arginine, phosphoric acid (to adjust pH), polysorbate 80, and nitrogen.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2-8°C (Refrigerate. Do not freeze.)

Chemical and physical in-use stability

The reconstituted solution may be stored for up to 24 hours at 2-8°C.

Microbiological in-use stability

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, the reconstituted solution should be stored at 2-8°C for not more than 24 hours.

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

6.5 NATURE AND CONTENTS OF CONTAINER

ACTILYSE CATHFLO is available in boxes containing either:

- 1 vial of ACTILYSE CATHFLO 2 mg in up to 93.3 mg dry powder; or
- 5 vials of ACTILYSE CATHFLO 2 mg in up to 93.3 mg dry powder.

Each constituted vial will deliver 2 mg of alteplase.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

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

6.7 PHYSICOCHEMICAL PROPERTIES

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

4 June 2008

10 DATE OF REVISION

05 November 2024

Summary table of changes

Section changed	Summary of new information
4.2	Updated images in instructions for reconstituting ACTILYSE CATHFLO table