

## New Zealand Datasheet

### Name of Medicine

ACTILYSE<sup>®</sup> CATHFLO<sup>®</sup>

Alteplase (recombinant human tissue-type plasminogen activator: rt-PA)

### Presentation

ACTILYSE 2 mg: clear glass injection vial containing 2 mg alteplase as a sterile white to off-white and 2.2 ml ampoule of water for injection.

### Uses

#### Actions

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.

ACTILYSE CATHFLO is 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 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.

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 coprecipitation of plasminogen within the fibrin clot. As a result, ACTILYSE CATHFLO produces clot dissolution in vivo with minimal systemic effects.

#### Pharmacokinetics

ACTILYSE CATHFLO is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 mL/min.). The relevant plasma half-life T<sub>1/2</sub> alpha is 4 - 5 minutes. This means that after 20 minutes less than 10% of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured.

When ACTILYSE CATHFLO is administered for restoration of dysfunctional 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 30-60 minutes.

## Indications

ACTILYSE CATHFLO is indicated for 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.

## Dosage and Administration

For the thrombolytic treatment of occluded central venous access devices including those used for haemodialysis, a dose of up to 2 mg alteplase administered up to two times for any one 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 in 2 ml should be instilled into the dysfunctional central venous access device.

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

If central venous access device function 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).

## 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 the appropriate volume of sterile Water for Injections into the ACTILYSE CATHFLO dry powder vial.

For ACTILYSE CATHFLO:

- Reconstitute the ACTILYSE CATHFLO 2 mg injection vial with 2.2 ml sterile Water for Injections in the accompanying ampoule.
- Reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterile Water for Injections into the lyophilised cake. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. Excessive or vigorous shaking should be avoided.

It is important that ACTILYSE CATHFLO be reconstituted only with sterile 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 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. Before dilution or administration, the reconstituted preparation 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 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 dilution of the reconstituted solution with sterile 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 CATHFLO solution. Because ACTILYSE CATHFLO contains no preservatives, it should be reconstituted immediately before use.

### **Instructions for Administration**

1. Reconstitute the content of the ACTILYSE CATHFLO 2 mg injection vial to the final concentration of 1 mg alteplase per ml. 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 Reconstitution and Dilution).
2. Instil the appropriate dose of ACTILYSE CATHFLO into the dysfunctional central venous access device.
3. After 30 minutes of dwell time, assess catheter function 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 function 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 function 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 device remains dysfunctional, consider the need for device replacement.
6. If catheter function 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).

### **Contraindications**

ACTILYSE CATHFLO should not be administered to patients with known hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients

### **Warnings and Precautions**

The appropriate pack size of alteplase should be chosen carefully and in accordance with the intended use. The 2 mg dose of alteplase (ACTILYSE CATHFLO) is not suitable for use in the indications acute myocardial infarction, acute pulmonary embolism or acute ischaemic stroke.

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

#### **General**

The coadministration 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 reocclusion this should be administered separately after catheter function has been restored.

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 should not be applied during attempts to determine catheter occlusion. Excessive pressure should 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: 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 administered up to two times for any one occlusion. 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

Antibody formation in patients receiving one or more doses of alteplase for restoration of dysfunctional central venous access devices has not been studied. Although physiologically relevant plasma concentrations are not reached, hypersensitivity might occur. Anaphylactoid reactions associated with the administration of ACTILYSE CATHFLO 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 CATHFLO powder contains natural rubber (a derivative of latex) which may cause allergic reactions. If an anaphylactoid reaction occurs, the instillation should be discontinued and appropriate treatment should be initiated.

## **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.

## **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 nursing women.

## **Use in Children**

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.

## **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 Warnings and Precautions – Bleeding).

## **Carcinogenicity**

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

## **Genotoxicity**

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

## **Adverse Effects**

In principle, all side effects as found for the systemic application of alteplase may also occur during treatment of occluded catheters in cases where ACTILYSE CATHFLO reaches the systemic circulation (e.g. hypersensitivity, anaphylactoid reaction), however pharmacokinetic data indicate that physiologically relevant plasma concentrations are not reached using this dosage. In clinical trials investigating treatment of occluded catheters with ACTILYSE CATHFLO the following side effects were observed.

Infections and infestations:

- sepsis

General disorders and administration site conditions:

- catheter related complication
- pyrexia

Under systemic application of alteplase (i.e. high dose in thrombo-embolic indications), the following side effects have been reported:

Immune system disorders:

- anaphylactoid reactions, which are usually mild, but can be life threatening in isolated cases.

They may appear as

- rash
- urticaria
- bronchospasm
- angioedema

- hypotension
- shock or any other symptom associated with hypersensitivity.

Immune system disorders can be regarded dose-independent and have therefore been copied from the systemic application; they have however not been observed in clinical trials with ACTILYSE CATHFLO.

## Interactions

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.

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. 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.

## Overdosage

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.

## Pharmaceutical Precautions

ACTILYSE CATHFLO must be stored at 2-8°C in a refrigerator. Do not freeze.

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, the reconstituted solution should be stored at 2-8°C for not more than 24 hours.

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 instillation, protection from light is not necessary.

## Medicine Classification

Prescription Medicine

## Package Quantities

ACTILYSE CATHFLO is available in boxes containing either:

- 1 vial of ACTILYSE CATHFLO 2 mg in up to 93.3 mg dry powder and 1 ampoule of 2.2 ml sterile Water for Injections for reconstitution; or
- 5 vials of ACTILYSE CATHFLO 2 mg in up to 93.3 mg dry powder and 5 ampoules of 2.2 ml sterile Water for Injections for reconstitution.

## Further Information

ACTILYSE<sup>®</sup> and CATHFLO<sup>®</sup> are registered trademarks.

## Excipients

L-arginine, phosphoric acid, polysorbate 80. ACTILYSE CATHFLO may contain trace residues of gentamicin from the manufacturing process

## Clinical Trials

### Occluded central venous access devices including those used for haemodialysis

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 Dosage and 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 Dosage and 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) 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 Dosage and 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  $\geq 2$  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.

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