

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Actilyse Cathflo 2 mg, poeder voor oplossing voor injectie en infusie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with powder contains:
2 mg alteplase (corresponding to 1,160,000 IU)

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.

Each constituted vial will deliver 2 mg of alteplase.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection and infusion.

The powder is presented as a colourless to pale yellow lyophilizate cake. The reconstituted preparation is a clear and colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Thrombolytic treatment of occluded central venous access devices including those used for haemodialysis
The 2 mg vial is the only recommended presentation of alteplase for use in this indication.

4.2 Posology and method of administration

Actilyse Cathflo should be given as early as possible after occlusion. The following dose guidelines apply.

Posology

A dose of up to 2 mg alteplase instilled in an occluded central venous access device 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.

For use in this indication reconstitution to a final concentration of 1 mg alteplase per ml is recommended. In patients with a body weight of 30 kg or more, a total dose of up to 2 mg alteplase in 2 ml of reconstituted solution 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 of alteplase per each instillation must not exceed 2 mg. I.e. for a catheter with internal volume of 1.0 ml the total dose of Actilyse Cathflo would be 1.1 mg in a volume of 1.1 ml.

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.

Paediatric population

The Paediatric population is covered by the general dosing scheme as described above.

Method of catheter clearance

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

Only 2 mg vials of alteplase are indicated for use in this indication. For instructions on how to reconstitute the product prior to administration, see section 6.6.

1. Reconstitute the content of an injection vial to a final concentration of 1 mg alteplase per ml. For catheters with a lumen volume greater than 2 ml, the reconstituted solution can be further diluted with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection to the desired volume. I.e. for a catheter with internal volume of 2.5 ml the total dose of Actilyse Cathflo would be 2.0 mg in a volume of 2.5 ml.
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 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 alteplase the catheter functionality has not been restored consider catheter replacement.
6. If catheter functionality has been restored, aspirate 4–5 ml of blood in patients weighing 10 kg or more, or 3 ml in patients with a body weight below 10 kg to remove Actilyse Cathflo and residual clot, and gently irrigate the catheter with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to gentamicin (a trace residue from the manufacturing process).

4.4 Special warnings and precautions for use

Traceability

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

The appropriate pack size of alteplase product should be chosen carefully and in accordance with the intended use. The 2 mg vial of alteplase 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 or 50 mg vials are indicated for use in those indications.

Coinstillation of heparin

The coinstillation of heparin with alteplase 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 alteplase is instilled into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the circulation.

Particular caution is necessary if small volume syringes (≤ 1 ml) are used for application, especially if small volume catheters are used as typical in the paediatric population.

Bleeding

The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. Alteplase 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 or who have had any of the following within 48 hours before start of instillation: surgery, obstetrical delivery, percutaneous biopsy of viscera or deep tissues, or puncture of non-compressible vessels. In addition, caution should be exercised with patients who have thrombocytopenia, other haemostatic defects (including those secondary to severe hepatic or renal disease), or 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 for 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 alteplase should be stopped and the drug should be withdrawn from the catheter.

Infection

Using alteplase in patients whose catheters are occluded by infected thrombi may release microorganisms 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.

Hypersensitivity

Antibody formation in patients receiving one or more doses of alteplase for restoration of occluded central venous access devices has not been studied. Hypersensitivity reactions associated with the instillation of alteplase can be caused by the active substance alteplase, gentamicin (a trace residue from the manufacturing process), or any of the excipients.

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

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Actilyse Cathflo have been performed.

Drugs affecting coagulation/platelet function

The risk of haemorrhage is increased if coumarine derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or other agents inhibiting coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse Cathflo).

ACE inhibitors

Concomitant treatment with ACE inhibitors may enhance the risk of suffering a hypersensitivity reaction.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of alteplase 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 unknown whether alteplase is excreted into human milk and there is insufficient information on the excretion of alteplase in animal milk.

Caution should be exercised when Actilyse Cathflo is used for a nursing woman and a decision must be made whether breast-feeding should be discontinued for the first 24 hours after use of Actilyse Cathflo.

Fertility

Clinical data on fertility are not available for Actilyse Cathflo. Non-clinical 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

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

In clinical trials investigating treatment of occluded catheters with Actilyse Cathflo the following adverse reactions were observed:

Class	Adverse reaction
Infections and infestations	
uncommon	sepsis
General disorders and administration site conditions	
uncommon	catheter related complication
rare	pyrexia

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

Immune system disorders	
rare	hypersensitivity reactions (e.g. rash, urticaria, bronchospasm, angio-oedema, hypotension, shock)*
very rare	serious anaphylaxis

*See sections 4.4 and 4.5

In principle, all undesirable effects as found for the systemic application of Actilyse (using the 10, 20, 50 mg vials of alteplase, please refer to respective SmPC) 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 reactions, blood pressure decreased, nausea, vomiting, body temperature increased). However, pharmacokinetic data indicate that physiologically relevant plasma concentrations are not reached using this dosage.

Immune system disorders, on the other hand, can be regarded dose-independent and have therefore been copied from the systemic application; immune system disorders have however not been observed in clinical trials with Actilyse Cathflo.

Paediatric Population

Based on clinical study data, the safety profile for use in children is comparable with the one observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

The relative fibrin specificity notwithstanding, a clinical 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 Cathflo therapy has been terminated. If, however, severe bleeding results, the infusion of fresh frozen plasma 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

Alteplase is 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

Occluded central venous access devices including those used for haemodialysis

In two clinical studies more than 1,100 mainly adult patients with improperly functioning central venous access devices were treated with alteplase. Restoration rates of catheter function were between 74 % and 77 % following one dose and between 87 % and 90 % following two doses of alteplase. In studies with

haemodialysis catheters using dwell times ranging from ≥ 2 hours to the next dialysis session comparable restoration rates were reported.

Paediatric population

In a study of 310 children the overall rate of catheter function restoration of 83 % after up to two doses of alteplase was similar to that observed in adults. A total of 432 patients under age of 17 have received a dose of up to 2 mg alteplase for up to two administrations in pivotal trials of catheter clearance. Overall safety and efficacy results were similar in the paediatric and adult patients.

5.2 Pharmacokinetic properties

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 ml/min.). Under physiological conditions, the major portion of alteplase in the circulation is inhibitor-bound. Hepatic clearance of alteplase is not hindered by the presence of other proteins including alteplase inhibitors. Complexes of alteplase and its inhibitor are eliminated as free alteplase. The relevant plasma half-life $t_{1/2}$ 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 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 30-60 minutes.

5.3 Preclinical safety data

In subchronic toxicity studies in rats and marmosets no unexpected undesirable effects 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

Powder:

Arginine

Phosphoric acid (for pH-adjustment)

Polysorbate 80

6.2 Incompatibilities

The reconstituted solution may be diluted with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg alteplase per ml since the occurrence of turbidity of the reconstituted solution cannot be excluded.

Further dilution, the use of water for injections for dilution 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 Cathflo should not be mixed with other medicinal products (not even with heparin).

6.3 Shelf life

Unopened vials

3 years

Reconstituted solution

The reconstituted solution has been demonstrated to be stable for 24 hours at 2 °C – 8 °C and for 8 hours at 25 °C.

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

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Store in a refrigerator (2 – 8 °C).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:

2 ml sterilised glass vials, sealed with sterile siliconised grey butyl-type stoppers with aluminium/plastic flip-off caps.

Pack sizes:


5 vials with 93 mg powder for solution for injection and infusion



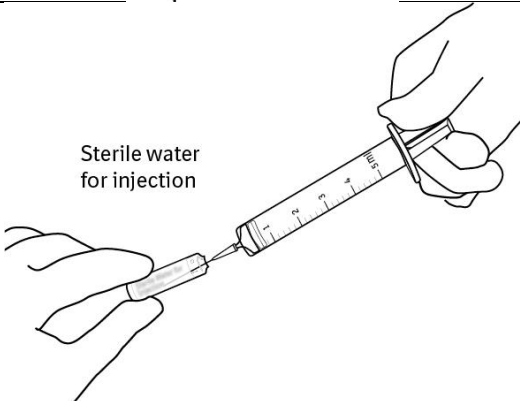
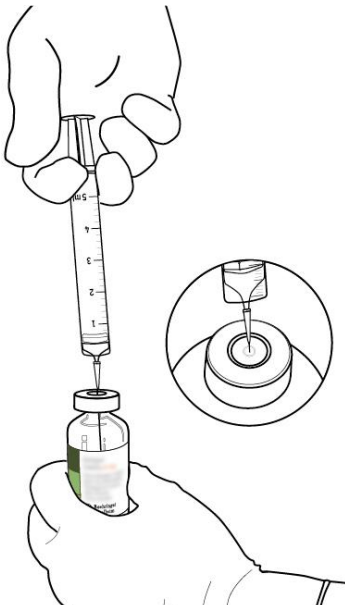
6.6 Special precautions for disposal and other handling

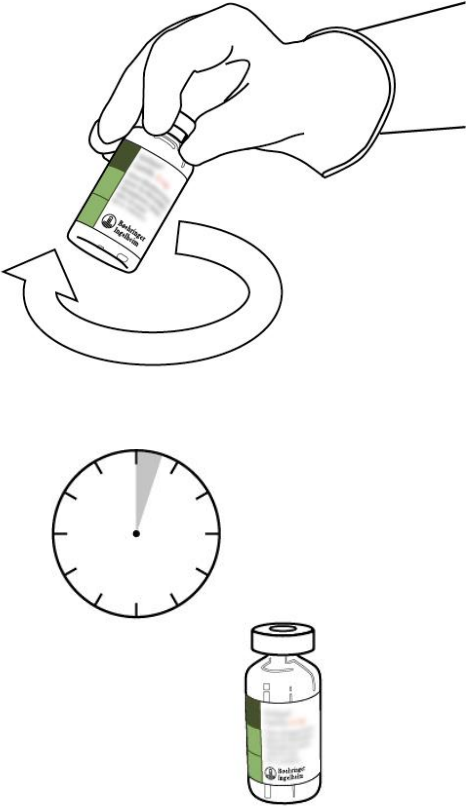
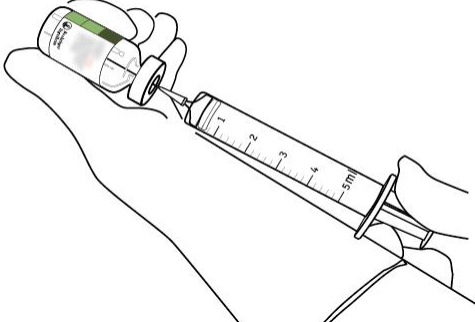
The 2 mg vial of alteplase is not indicated for use in myocardial infarction, acute pulmonary embolism or acute ischaemic stroke (due to risk of massive underdosing). Only 10, 20 or 50 mg vials are indicated for use in those indications.

The 2 mg vial (supplied with an overage) is dissolved with 2.2 mL sterilised water for injection to obtain a final concentration of 1 mg alteplase per ml.

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	Withdraw 2.2 mL sterilised water for injection by use of a syringe with a suitable measuring precision under aseptic conditions.	 <p data-bbox="874 1070 999 1122">Sterile water for injection</p>
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.	

<p>6</p>	<p>Take the vial with reconstituted Actilyse Cathflo and swirl gently to dissolve any remaining powder, but do not shake, as this will produce foam.</p> <p>If there are bubbles, let the solution stand undisturbed for a few minutes to allow them to disappear.</p>	
<p>7</p>	<p>The reconstituted solution consists of 1 mg/mL alteplase. It should be clear and colourless to pale yellow and it should not contain any particles.</p>	
<p>8</p>	<p>Remove the amount required using a needle and a syringe.</p>	
<p>9</p>	<p>Use immediately. Any unused medicinal product or waste material should be disposed in accordance with the local requirements.</p>	

The reconstituted solution should then be instilled into the occluded central venous access device. It 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 Cathflo should not be mixed with other medicinal products in the same catheter (not even with heparin).

For incompatibilities see section 6.2.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim bv
Comeniusstraat 6
1817 MS ALKMAAR

8. MARKETING AUTHORISATION NUMBER(S)

Actilyse Cathflo 2 mg, poeder voor oplossing voor injectie en infusie: RVG 103374

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 Augustus 2008
Date of last renewal: 26 April 2009

10. DATE OF REVISION OF THE TEXT

Laatst gedeeltelijke wijziging betreft rubrieken 4.2, 4.4, 4.6, 5.2 en 6.6: 11 januari 2022