Hold ourselves accountable to the standard of care

Use evidence-based guidelines to deliver quality care to patients with central lines
Central Venous Access Devices (CVADs) deliver life-sustaining therapies

An evidence-based list of indications for CVAD use include, but are not limited to¹:

1. Clinical instability of the patient and/or complexity of infusion regimen (multiple infusates)

2. Episodic chemotherapy treatment anticipated for more than 3 months

3. Prescribed continuous infusion therapy (e.g., parenteral nutrition, fluid and electrolytes, medications, blood or blood products)

4. Invasive hemodynamic monitoring

5. Long-term intermittent infusion therapy (e.g., any medication including anti-infectives in patients with a known or suspected infection)

6. History of failed or difficult peripheral venous access, if use of ultrasound guidance has failed

Catheters can be used either short or long term for the infusion of¹-³

- Antibiotics
- Parenteral nutrition
- Medication/solutions in patients with limited peripheral access
- Chemotherapy or other vesicant or irritating solutions
- Blood and blood products
- Therapy that is ongoing or continued at home
Why is it important to ensure central line patency?

An occluded line may complicate patient care by\textsuperscript{3-5}:

- Disrupting therapies or delaying procedures
- Interrupting administration of medications and solutions
- Delays in discharge
- Additional procedures, such as catheter replacement

“Foster a just culture and individual accountability through a focus on improving systems and processes by clinicians and leaders.”\textsuperscript{1}

INS Infusion Therapy Standards of Practice, 2016, page S21, standard 6A

“Catheter salvage is preferred over catheter removal for management of CVAD occlusions.”\textsuperscript{1}

INS Infusion Therapy Standards of Practice, 2016, page S104, standard 48.3

INS=Infusion Nurses Society.
CVADs provide access to central venous circulation

Central venous access devices are:
- Also known as central venous catheters (CVC) or central lines
- A mainstay for patients requiring intravenous (IV) administration of medications and other fluids
- Tip of a CVAD generally placed in the lower third of the superior vena cava (SVC), near its junction with the right atrium\(^1,2\)
- Blood flow rate in SVC is approximately 2 liters per minute\(^6\)
- In SVC, infusates are rapidly hemodiluted and distributed in the central venous system

CVAD insertion and tip sites\(^1,7\)
Types of CVADs

**Peripherally inserted central catheters (PICCs)***
- Can be used for a variety of IV therapies
- May be used for blood sampling with proper technique
- Can be used in a variety of care settings across diverse patient populations
- May be placed bedside or in an outpatient setting

**Nontunneled catheters***
- Also called subclavian, percutaneous, or short-term catheters
- Typically used for days or weeks for all types of IV therapy, to draw blood, and to monitor central venous pressure
- May be placed bedside or, if necessary, in an emergency setting, without sedation

**Tunneled catheters***
- Designed for long-term use and frequent venous access
- Provide reliable IV access for extended courses of antibiotics, chemotherapy, and parenteral nutrition
- Surgically inserted

**Implanted ports***
- Consist of 2 attached parts: the catheter and portal body with reservoir
- Long-term dwell capacity, requiring little maintenance when not in use
- Useful for cyclically infused therapies, such as chemotherapy
- Blood draws may also be done through the port

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(A) © 2012 C. R. Bard, Inc. Used with permission. Bard is a registered trademark of C. R. Bard, Inc.
(B) Please be advised: the port shown is manufactured by VATA but is not for implantation in humans or animals and is only supplied non-sterile. Port is for use in simulation training/practice only.
Catheter occlusion is the most common noninfectious complication in the long-term use of CVADs\(^8\)\(^9\)

- Occlusions may occur in up to 25% of CVADs\(^8\)
- May occur soon after insertion of a device or develop at any time\(^10\)

Causes of catheter occlusions

- About 58% of catheter occlusions are thrombotic\(^8\)
- Thrombotic occlusions result from the formation of a thrombus within, surrounding, or at the tip of the catheter\(^8,10\)
- About 42% of catheter occlusions are due to nonthrombotic causes, including precipitates, malpositioning, mechanical obstructions, and other factors\(^8,10\)

Data in this section derived from a study of 200 dysfunctional catheters in 172 adult patients.\(^6\)

"Catheter occlusions are categorized as thrombotic or nonthrombotic, and an accurate diagnosis of the type of occlusion is essential for appropriate treatment."\(^11\)
Nonthrombotic catheter occlusions

Mechanical occlusions

- Mechanical occlusions may result from malposition during insertion and use, or catheter migration
- Factors influencing the incidence of malposition include an increase in intrathoracic pressure from coughing, sneezing, or vomiting; arm movements; forceful flushing of the catheter; and thrombus formation

Precipitates

- Precipitates can form as a result of drug crystallization, drug-drug incompatibilities, or drug-solution incompatibilities
- Drug precipitates in the catheter may occur in conjunction with thrombus formation and should always be considered during assessment of an occlusion, since this may have implications for how the occlusion should be managed

Lipid residue

- Lipid residue can accumulate in central venous catheters, often following the administration of lipid-containing, three-in-one total parenteral nutrition admixtures or drugs with oleaginous vehicles

Salvaging catheters with nonthrombotic occlusions

- In many instances, mechanical problems, such as kinked tubing or clogged in-line filters, can be identified and corrected
  - Possible interventions to reposition catheters include patient positioning, rapid flushing of the catheter guidewire catheter exchange, fluoroscopic catheter guidance, or partial catheter withdrawal
- Catheters occluded by calcium-phosphate precipitates can be treated with 0.1 N hydrochloric acid
- Sodium bicarbonate (1 mEq/mL) is used for substances known to dissolve in an alkaline environment
- Lipid occlusions have been treated with ethanol (70%) or sodium hydroxide (0.1 mmol/mL)
- The use of incompatible drugs or solutions should be avoided
Thrombotic catheter occlusions

When introduced into the body, all catheters begin to accumulate fibrin

This is the body’s natural attempt to protect itself against a foreign body. The fibrin starts to form a layer around the outside of the catheter within minutes of insertion, beginning at either the line entry site or where the tip contacts the vein.\(^4,13\)

Fibrin tail, or flap\(^5\)

- Extends from the catheter tip but is drawn inward, blocking the opening of the catheter lumen on aspiration attempts
- Results in an ability to infuse fluids but an inability to withdraw blood

Intraluminal thrombus\(^5\)

- Occurs when blood refluxes inside the catheter lumen
- Common causes of reflux include coughing, inadequate flushing after blood draws or after checking for blood return, or improper use of flush syringes

Mural thrombus\(^3-5\)

- Forms where the catheter touches or “rubs” the vein wall
- Common sites are the entry site, anywhere along the catheter path, and the catheter tip

Fibrin sheath\(^4,5\)

- Forms when fibrin adheres to the external catheter surface, which may include the entry site, and may encase all or part of the catheter like a sock
- May completely cover the opening of the catheter tip
Catheter occlusions can be partial or complete

- Partial occlusion: ability to infuse but not withdraw fluids, or the presence of sluggish flow*
- Complete occlusion: inability to infuse or aspirate

Partial occlusion

Complete occlusion

Aspirating for a positive blood return may reveal a partial occlusion

- Fibrin tail allowing infusion
- Beginning to flap back with start of withdrawal
- Blocking aspiration of the catheter

Flushing the line is not enough—you must be able to withdraw blood to rule out a partial occlusion before administering critical therapies.¹

*One quantitative measure for sluggish flow is a blood return of less than 3 mL in 3 seconds, as recommended by the Oncology Nursing Advisory Board.¹³
Recognizing signs of CVAD occlusion

With a blood flow through the SVC of approximately 2 liters per minute<sup>6</sup>

A free-flowing blood return should be readily achievable. Lack of blood return or a sluggish flow may indicate a catheter occlusion or a malpositioned tip, and further assessment of the line will be necessary.<sup>1</sup>

**Signs of a CVAD occlusion include**<sup>1</sup>

- Inability to withdraw blood or sluggish blood return
- Sluggish flow
- Inability to flush or infuse through the CVAD
- Frequent occlusion alarms on electronic infusion device
- Infiltration/extravasation or swelling/leaking at the infusion site

**CVAD occlusions should not be left untreated because another lumen is patent.**<sup>1</sup>

INS Infusion Therapy Standards of Practice, 2016, page S104, standard 48, practice criterion D
Recommended routine assessment of catheter patency

“Ensure brisk blood return. Ensure consistent verification of blood return prior to, during, and after infusion.”

ONS Access Device Standards of Practice, 2017, page 94, standard H3, b

Prior to the administration of any medications or solutions, the nurse should always

- Aspirate for a positive blood return that is the color and consistency of whole blood
- Check for other indications of an occlusion
- Attempt to flush to determine resistance, flushing with an adequate volume of saline or appropriate solution
- Palpate the insertion site to determine tenderness
- Assess the patient for any pain or discomfort

Documentation of CVAD patency is a clinical practice standard and should include

- Device patency
- Absence of signs and symptoms of complications
- Lack of resistance when flushing
- Presence of a blood return upon aspiration

ONS=Oncology Nursing Society.
Recommended algorithm for assessing and treating occluded catheters

Indication
Cathflo® Activase® (alteplase) is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

Important Safety Information

Contraindications
Cathflo Activase should not be administered to patients with known hypersensitivity to alteplase or any component of the formulation.

Precautions

General
Certain causes of catheter dysfunction should be considered before treatment with Cathflo Activase (e.g. catheter malposition, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen). These types of conditions should be considered before treatment with Cathflo Activase. Excessive pressure should be avoided when Cathflo Activase 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. Cathflo Activase has not been studied in patients 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 any condition for which bleeding constitutes a significant hazard. Should serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

Infections
Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation. As with all catheterization procedures, care should be used to maintain aseptic technique.

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.
Cathflo 2 mg: the standard of care for the treatment of thrombotically occluded catheters

Cathflo is the only FDA-approved thrombolytic agent for the restoration of function to CVADs as assessed by the ability to withdraw blood\textsuperscript{14}

Cathflo is the only thrombolytic recommended by clinical practice standards\textsuperscript{1,7,9,14}

- Infusion Nurses Society (INS)
- Association for Vascular Access (AVA)
- American Association of Critical Care Nurses (AACN)
- Oncology Nursing Society (ONS)

A fibrin-specific* MOA\textsuperscript{15}

- The fibrin-specific mechanism of action (MOA) addresses the root cause of thrombotic occlusions
- Cathflo binds to fibrin in the thrombus, converting entrapped plasminogen to plasmin, initiating local fibrinolysis

Pharmacokinetics

- When Cathflo 2 mg is administered according to the instructions for dosing and administration, circulating plasma levels of alteplase are not expected to reach pharmacologic concentrations\textsuperscript{15}

\begin{itemize}
\item [1] Recombinant t-PA (alteplase) binds to fibrin in thrombus
\item [2] Converting entrapped plasminogen to plasmin
\item [3] Initiate local fibrinolysis
\end{itemize}

*The clinical significance of fibrin specificity is unknown.
Cathflo Activase (alteplase) 2 mg is integral to evidence-based practices for treating thrombotically occluded catheters

- In the pivotal trials COOL-1 and COOL-2, the efficacy of Cathflo was evaluated in 1122 primarily adult patients\textsuperscript{15}

**Cumulative efficacy**

In COOL-1, Cathflo restored function to 88% (112/127) of central lines after up to 2 doses using a 120-minute dwell time for each in catheters with occlusions present for up to 24 hours.

In COOL-1 and COOL-2, Cathflo restored function to 68% (796/1043) of central lines after 1 dose and 88% (902/1043) of central lines after 2 doses in catheters with occlusions present for less than 14 days.

**First-dose efficacy**

In COOL-2, Cathflo restored function after 1 dose in 75% (747/995) of central lines after up to 120 minutes of dwell time in catheters with occlusions present for any duration.

**Occlusions >14 days efficacy**

In COOL-2, Cathflo restored function to 57% (30/53) of central lines after 1 dose and 72% (38/53) of central lines after up to 2 doses in catheters with occlusions present for longer than 14 days.

**Maintained patency**

In a subset of patients (n=346) who had a successful treatment outcome, 74% (256/346) of central lines maintained patency up to 30 days after treatment with Cathflo.

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**Important Safety Information (cont’d)**

**Hypersensitivity**

Hypersensitivity, including urticaria, angioedema and anaphylaxis, has been reported in association with use of Cathflo Activase. Monitor patients treated with Cathflo Activase for signs of hypersensitivity and treat appropriately if necessary.

**Drug Interactions and Drug/Laboratory Test Interactions**

The interaction of Cathflo Activase with other drugs has not been formally studied. Concomitant use of drugs affecting coagulation and/or platelet function has not been studied. Potential interactions between Cathflo Activase and laboratory tests have not been studied.

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.
Cathflo safety profile in adult and pediatric patients

Cathflo has a safety profile studied in both adult and pediatric patients.\textsuperscript{15,16}

- In the pivotal trials COOL-1 and COOL-2, the safety profile of Cathflo was evaluated in 1122 primarily adult patients\textsuperscript{15}
- CAPS evaluated the safety profile of Cathflo in 310 pediatric patients. Patient ages ranged from 2 weeks to 17 years\textsuperscript{15,16}

<table>
<thead>
<tr>
<th>COOL-1 and COOL-2 (N=1122) Serious adverse events\textsuperscript{15}</th>
<th>CAPS (N=310) Serious adverse events\textsuperscript{16}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis 0.4%</td>
<td>Catheter-related complications 1.3%*</td>
</tr>
<tr>
<td>Major hemorrhage 0.4%</td>
<td>Sepsis 1.0%</td>
</tr>
<tr>
<td>Gastrointestinal bleeding 0.3%</td>
<td>Fever &lt;1.0%</td>
</tr>
<tr>
<td>Venous thrombosis 0.3%</td>
<td>Intracranial hemorrhage 0.0%</td>
</tr>
<tr>
<td>Intracranial hemorrhage 0.0%</td>
<td>Major hemorrhage 0.0%</td>
</tr>
<tr>
<td>Embolic event 0.0%</td>
<td>Thrombosis 0.0%</td>
</tr>
<tr>
<td></td>
<td>Embolic event 0.0%</td>
</tr>
</tbody>
</table>

Adapted from Blaney M, et al.
*At least 1 due to catheter rupture.

No reports of intracranial hemorrhage or embolic events with Cathflo in clinical trials

CAPS=Cathflo Activase Pediatric Study.
CAPS was an open-label, single-arm trial that evaluated the safety of Cathflo in 310 patients between the ages of 2 weeks and 17 years. Cathflo was evaluated in a maximum of 2 doses at ≤2 mg per dose. The primary objective was to evaluate safety, as measured by the incidence of intracranial hemorrhage (ICH). Secondary objectives included assessing restoration rates at 30 minutes and 120 minutes, and serious adverse events within 48 hours.\textsuperscript{15,16}

Use 2 mg alteplase (Cathflo Activase) to restore patency and maintain catheter function.\textsuperscript{7}

Practice Standard, ONS Access Device Standards of Practice, 2017, page 10, section VI, Practice Standard B
Dosing and administration of Cathflo Activase (alteplase) 2 mg

Administration\textsuperscript{15}

After WASHING hands and applying gloves:

1. After reconstitution using 2.2 mL sterile water for injection and aseptic technique, INSPECT solution for foreign matter and discoloration.

2. INSTILL the appropriate dose of Cathflo into the occluded catheter using a 10-mL syringe (see dosing chart on the following page).

3. After 30 minutes of DWELL time, assess catheter function by attempting to aspirate blood. If the catheter is functional, go to step 5; if not functional, go to step 4.

4. ASSESS catheter function after a total of 120 minutes of dwell time by attempting to aspirate blood. If catheter is functional, go to step 5. If catheter is still occluded, a second dose of equal amount may be instilled. Repeat steps 1 through 3.

5. If catheter function has been restored, ASPIRATE 4 mL to 5 mL of blood in patients ≥10 kg or 3 mL in patients <10 kg to remove Cathflo and residual clot. Then discard aspirate, and flush the catheter with 0.9% Sodium Chloride, USP. Any unused solution should be discarded.

Important Safety Information (cont’d)

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Cathflo Activase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions

In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding, and venous thrombosis.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.
FDA-approved dosing with Cathflo 2 mg

- Cathflo is available in a single-use, 2-mg vial and it is not recommended that it be compounded, frozen, or thawed.
- If catheter function is not restored at 120 minutes after 1 dose of Cathflo, a second dose may be instilled.*

*Studies only evaluated up to two 2-mg doses.

Cathflo Dosing Chart

<table>
<thead>
<tr>
<th>PATIENT WEIGHT</th>
<th>CATHFLO DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 kg (66 lb)</td>
<td>2 mg in 2 mL</td>
</tr>
<tr>
<td>&lt;30 kg (66 lb)</td>
<td>110% of the internal lumen volume of CVAD, not to exceed 2 mg in 2 mL</td>
</tr>
</tbody>
</table>

Note: Store lyophilized Cathflo at refrigerated temperature (2°C–8°C/36°F–46°F). Cathflo should be reconstituted immediately before use. The solution may be used within 8 hours if stored at 2°C to 30°C (36°F–86°F). No other medication should be added to solutions containing Cathflo.

The instillation of alteplase 2 mg (Cathflo Activase) is effective in restoring catheter patency in patients.¹

INS Infusion Therapy Standards of Practice, 2016, page S105, standard 48, practice criterion G

Visit Cathflo.com to order and download additional tools and educational resources.

Is your hospital delivering the standard of care for patients with central lines?

- Utilize the highest level of evidence available for central line care and maintenance
- Include patency checks in central line care protocols and maintenance bundle
- Develop a culture of accountability using CVAD quality metrics and EHR documentation

**Indication**
Cathflo® Activase® (alteplase) is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

**Important Safety Information**

**Contraindications**
Cathflo Activase should not be administered to patients with known hypersensitivity to alteplase or any component of the formulation.

**Precautions**

**General**
Certain causes of catheter dysfunction should be considered before treatment with Cathflo Activase (e.g. catheter malposition, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen). These types of conditions should be considered before treatment with Cathflo Activase.

**Bleeding**
The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. Should serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

**Infections**
Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter.

**Hypersensitivity**
Hypersensitivity, including urticaria, angioedema and anaphylaxis, has been reported in association with use of Cathflo Activase. Monitor patients treated with Cathflo Activase for signs of hypersensitivity and treat appropriately if necessary.

**Adverse Reactions**
In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding, and venous thrombosis.

Please see accompanying full Prescribing Information for additional Important Safety Information.

To learn more about the management of thrombotically occluded catheters, please visit www.cathflo.com or call Genentech Customer Service at 1-800-551-2231 to locate your local Genentech clinical specialist.
Cathflo® Activase®
(Alteplase)

Powder for reconstitution for use in central venous access devices

DESCRIPTION
Cathflo® Activase® (Alteplase) is a tissue plasminogen activator (t-PA) produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator (t-PA) obtained from an established human cell line. The manufacturing process involves secretion of the enzyme Alteplase into the culture medium by an established mammalian cell line (Chinese hamster ovary cells) into which the cDNA for Alteplase has been genetically inserted.

Cathflo Activase (Alteplase) for injection is a sterile, white to pale yellow, lyophilized powder for intracatheter instillation for restoration of function to central venous access devices following reconstitution with Sterile Water for Injection, USP.

Each vial of Cathflo Activase contains 2.2 mg of Alteplase (which includes a 10% overfill), 77 mg of L-arginine, 0.2 mg of polysorbate 80, and phosphoric acid for pH adjustment. Each reconstituted vial will deliver 2 mg of Cathflo Activase, at a pH of approximately 7.3.

CLINICAL PHARMACOLOGY
Alteplase is an enzyme (serine protease) that has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. Alteplase
binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin, thereby initiating local fibrinolysis (1).

In patients with acute myocardial infarction administered 100 mg of Activase as an accelerated intravenous infusion over 90 minutes, plasma clearance occurred with an initial half-life of less than 5 minutes and a terminal half-life of 72 minutes. Clearance is mediated primarily by the liver (2).

When Cathflo Activase is administered for restoration of function to central venous access devices according to the instructions in DOSAGE AND ADMINISTRATION, circulating plasma levels of Alteplase are not expected to reach pharmacologic concentrations. If a 2 mg dose of Alteplase were 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 endogenous circulating levels of 5–10 ng/mL within 30 minutes (1).

CLINICAL STUDIES
Three clinical studies were performed in patients with improperly functioning central venous access devices (CVADs).

A placebo-controlled, double-blind, randomized trial (Trial 1) and a larger open-label trial (Trial 2) investigated the use of Alteplase in predominately adult patients who had an indwelling CVAD for administration of chemotherapy, total parenteral nutrition, or long-term administration of antibiotics or other medications. Both studies enrolled patients whose catheters were not functioning (defined as the inability to withdraw at least 3 mL of blood from the device) but had the ability to instill the necessary volume of study drug. Patients with hemodialysis catheters or a known
mechanical occlusion were excluded from both studies. Also excluded were patients considered at high risk for bleeding or embolization (see PRECAUTIONS, Bleeding), as well as patients who were younger than 2 years old or weighed less than 10 kg. Restoration of function was assessed by successful withdrawal of 3 mL of blood and infusion of 5 mL of saline through the catheter.

Trial 1 tested the efficacy of a 2 mg/2 mL Alteplase dose in restoring function to occluded catheters in 150 patients with catheter occlusion up to 24 hours in duration. Patients were randomized to receive either Alteplase or placebo instilled into the lumen of the catheter, and catheter function was assessed at 120 minutes. Restoration of function was assessed by successful withdrawal of 3 mL of blood and infusion of 5 mL of saline through the catheter. All patients whose catheters did not meet these criteria were then administered Alteplase, until function was restored or each patient had received up to two active doses. After the initial dose of study agent, 51 (67%) of 76 patients randomized to Alteplase and 12 (16%) of 74 patients randomized to placebo had catheter function restored. This resulted in a treatment-associated difference of 51% (95% CI is 37% to 64%). A total of 112 (88%) of 127 Alteplase-treated patients had restored function after up to two doses.

Trial 2 was an open-label, single arm trial in 995 patients with catheter dysfunction and included patients with occlusions present for any duration. Patients were treated with Alteplase with up to two doses of 2 mg/2 mL (less for children who weighed less than 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. Thirty minutes after instillation of the first dose, 516 (52%) of 995 patients had restored catheter function. One hundred twenty minutes after the instillation of the first dose, 747 (75%) of 995 patients had restored catheter function. If function was not restored after the first dose, a second dose was administered. Two hundred nine patients received a second dose. Thirty minutes after instillation of the second dose, 70 (33%) of 209 patients had restored catheter function. One hundred twenty minutes after the instillation of the second dose, 97 (46%) of 209 patients had restored catheter function. A total of 844 (85%) of 995 patients had function restored after up to 2 doses.

Across Trials 1 and 2, 796 (68%) of 1043 patients with occlusions present for less than 14 days had restored function after one dose, and 902 (88%) had function restored after up to two doses. Of 53 patients with occlusions present for longer than 14 days, 30 (57%) patients had function restored after a single dose, and a total of 38 patients (72%) had restored function after up to two doses.

Three hundred forty-six patients who had successful treatment outcome were evaluated at 30 days after treatment. The incidence of recurrent catheter dysfunction within this period was 26%.

Trial 3 was an open-label, single-arm trial in 310 patients between the ages of 2 weeks and 17 years. All patients had catheter dysfunction defined as the inability to withdraw blood (at least 3 mL for patients ≥ 10 kg or at least 1 mL for patients < 10 kg). Catheter dysfunction could be present for any duration. The indwelling CVADs (single-, double-, and triple-lumen, and implanted ports) were used for administration of chemotherapy, blood products or fluid replacement, total parenteral
nutrition, antibiotics, or other medications. Patients with hemodialysis catheters or known mechanical occlusions were excluded from the study, as were patients considered at high risk for bleeding or embolization.

Patients were treated with up to two doses of Cathflo Activase instilled into the catheter lumen. For patients weighing ≥ 30 kg, the dose was 2 mg in 2 mL. For patients weighing < 30 kg, the dose was 110% of the estimated internal lumen volume, not to exceed 2 mg in 2 mL. Restoration of function was assessed at 30 and 120 minutes (if required) after administration of each dose. Restoration of function was defined as the ability to withdraw fluid (3 mL in patients ≥ 10 kg; 1 mL in patients < 10 kg) and infuse saline (5 mL in patients ≥ 10 kg; 3 mL in patients < 10 kg).

The overall rate of catheter function restoration of 83% (257 of 310) was similar to that observed in Trial 2, as were the rates of function restoration at the intermediate assessments.

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.

INDICATIONS AND USAGE

Cathflo® Activase® (Alteplase) is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.
CONTRAINDICATIONS
Cathflo Activase should not be administered to patients with known hypersensitivity to Alteplase or any component of the formulation (see DESCRIPTION).

WARNINGS
None.

PRECAUTIONS
General
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. These types of conditions should be considered before treatment with Cathflo Activase.

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 Cathflo Activase 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 (3,4). Cathflo Activase has not been studied in patients 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: 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 hemostatic 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 Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

**Infections**

Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation (see ADVERSE REACTIONS). As with all catheterization procedures, care should be used to maintain aseptic technique.

**Hypersensitivity**

Hypersensitivity, including urticaria, angioedema and anaphylaxis, has been reported in association with use of Cathflo Activase. Monitor patients treated with Cathflo Activase for signs of hypersensitivity and treat appropriately if necessary.
**Re-Administration**
In clinical trials, patients received up to two 2 mg/2 mL doses (4 mg total) of Alteplase. Additional re-administration of Cathflo Activase has not been studied. Antibody formation in patients receiving one or more doses of Cathflo Activase for restoration of function to CVADs has not been studied.

**Drug Interactions**
The interaction of Cathflo Activase with other drugs has not been formally studied. Concomitant use of drugs affecting coagulation and/or platelet function has not been studied.

**Drug/Laboratory Test Interactions**
Potential interactions between Cathflo Activase and laboratory tests have not been studied.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies that evaluated tumorigenicity of Alteplase and effect on tumor metastases were negative in rodents. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure at high concentrations exceeding those expected to be achieved with Cathflo Activase.

**Pregnancy**
Alteplase has been shown to have an embryocidal effect due to an increased postimplantation loss rate in rabbits when administered intravenously during organogenesis at a dose (3 mg/kg) approximately 50
times human exposure (based on AUC) at the dose for restoration of function to occluded CVADs. No maternal or fetal toxicity was evident at a dose (1 mg/kg) approximately 16 times human exposure at the dose for restoration of function to occluded CVADs.

There are no adequate and well-controlled studies in pregnant women. Cathflo Activase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether Cathflo Activase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cathflo Activase is administered to a nursing woman.

**Pediatric Use**

A total of 432 subjects under age 17 have received Cathflo Activase in the three trials. Rates of serious adverse events were similar in the pediatric and adult patients, as were the rates of catheter function restoration.

**Geriatric Use**

In 312 patients enrolled who were age 65 years and over, no incidents of intracranial hemorrhage (ICH), embolic events, or major bleeding events were observed. One hundred three of these patients were age 75 years and over, and 12 were age 85 years and over. The effect of Alteplase on common age-related comorbidities has not been studied. In general, caution should be used in geriatric patients with conditions known to increase the risk of bleeding (see PRECAUTIONS, Bleeding).

**ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in Section PRECAUTIONS of the label:
- Bleeding
- Hypersensitivity

In the clinical trials, the most serious adverse events reported after treatment were sepsis (see PRECAUTIONS, Infections), gastrointestinal bleeding, and venous thrombosis.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Trials 1 and 2**

The data described for Trials 1 and 2 reflect exposure to Cathflo Activase in 1122 patients, of whom 880 received a single dose and 242 received two sequential doses of Cathflo Activase.

In the Cathflo Activase Trials 1 and 2, only limited, focused types of serious adverse events were recorded, including death, major hemorrhage, intracranial hemorrhage, pulmonary or arterial emboli, and other serious adverse events not thought to be attributed to underlying disease or concurrent illness. Major hemorrhage was defined as severe blood loss (> 5 mL/kg), blood loss requiring transfusion, or blood loss causing hypotension. Non-serious adverse events and serious events thought to be due to underlying disease or concurrent illness were not recorded. Patients were observed for serious adverse events until catheter function was deemed to be restored or for a maximum of 4 or 6 hours depending on study. For most patients the observation period was 30 minutes to 2 hours. Spontaneously reported deaths and serious adverse events that were not thought to be related to the patient’s underlying disease were also recorded during the 30 days following treatment.
Four catheter-related sepsis events occurred from 15 minutes to 1 day after
treatment with Alteplase, and a fifth sepsis event occurred on Day 3 after
Alteplase treatment. All 5 patients had positive catheter or peripheral
blood cultures within 24 hours after symptom onset.

Three patients had a major hemorrhage from a gastrointestinal source from
2 to 3 days after Alteplase treatment. One case of injection site
hemorrhage was observed at 4 hours after treatment in a patient with
pre-existing thrombocytopenia. These events may have been related to
underlying disease and treatments for malignancy, but a contribution to
occurrence of the events from Alteplase cannot be ruled out. There were
no reports of intracranial hemorrhage.

Three cases of subclavian and upper extremity deep venous thrombosis
were reported 3 to 7 days after treatment. These events may have been
related to underlying disease or to the long-term presence of an indwelling
catheter, but a contribution to occurrence of the events from Alteplase
treatment cannot be ruled out. There were no reports of pulmonary
emboli.

There were no gender-related differences observed in the rates of adverse
reactions. Adverse reactions profiles were similar across all age
subgroups.

**Trial 3**

In Trial 3 all serious adverse events were recorded with a specific interest
in intracranial hemorrhage, major hemorrhage, thrombosis, embolic
events, sepsis and catheter related complications. Major hemorrhage was
defined as severe blood loss ( > 5 mL/kg), blood loss requiring transfusion,
or blood loss causing hypotension. Non-serious adverse events were not
recorded. Patients were observed until catheter function was deemed to be restored or for a maximum of 4 hours after the first dose. Additionally, serious adverse events were elicited from patients at 48 hours (up to 96 hours) following completion of treatment.

No pediatric patients in Trial 3 experienced an intracranial hemorrhage, major hemorrhage, thrombosis, or an embolic event.

Three cases of sepsis occurred 2 to 44 hours after treatment with Cathflo Activase. All of these patients had evidence of infection prior to administration of Cathflo Activase. An additional patient developed fever and lethargy within one day of Cathflo Activase administration, which required outpatient intravenous antibiotics. In one subject, the lumen of the catheter, placed 2 years previously, ruptured with infusion of the study drug.

There were no gender-related differences observed in the rates of adverse reactions. Adverse reactions profiles were similar across all age groups.

**DOSAGE AND ADMINISTRATION**

Cathflo® Activase® (Alteplase) is for instillation into the dysfunctional catheter at a concentration of 1 mg/mL.

- Patients weighing ≥30 kg: 2 mg in 2 mL
- Patients weighing <30 kg: 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL

If catheter function is not restored at 120 minutes after 1 dose of Cathflo Activase, a second dose may be instilled (see Instructions for Administration). 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 2-mg doses).

**Instructions for Administration**

*Preparation of Solution*

Reconstitute Cathflo Activase to a final concentration of 1 mg/mL:

1. Aseptically withdraw 2.2 mL of Sterile Water for Injection, USP (diluent is not provided). Do not use Bacteriostatic Water for Injection.

2. Inject the 2.2 mL of Sterile Water for Injection, USP, into the Cathflo Activase vial, directing the diluent stream into the powder. Slight foaming is not unusual; let the vial stand undisturbed to allow large bubbles to dissipate.

3. Mix by gently swirling until the contents are completely dissolved. Complete dissolution should occur within 3 minutes. **DO NOT SHAKE.** The reconstituted preparation results in a colorless to pale yellow transparent solution containing 1 mg/mL Cathflo Activase at a pH of approximately 7.3.

4. Cathflo Activase contains no antibacterial preservatives and should be reconstituted immediately before use. The solution may be used for intracatheter instillation within 8 hours following reconstitution when stored at 2–30°C (36–86°F).

**No other medication should be added to solutions containing Cathflo Activase.**

*Instillation of Solution into the Catheter*

1. Inspect the product prior to administration for foreign matter and discoloration.

2. Withdraw 2 mL (2 mg) of solution from the reconstituted vial.

3. Instill the appropriate dose of Cathflo Activase (see DOSAGE AND ADMINISTRATION) into the occluded catheter.
4. After 30 minutes of dwell time, assess catheter function by attempting to aspirate blood. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 5.

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

6. If catheter function is not restored after one dose of Cathflo Activase, a second dose of equal amount may be instilled. Repeat the procedure beginning with Step 1 under Preparation of Solution.

7. If catheter function has been restored, aspirate 4–5 mL of blood in patients ≥10 kg or 3 mL in patients <10 kg to remove Cathflo Activase and residual clot, and gently irrigate the catheter with 0.9% Sodium Chloride Injection, USP.

Any unused solution should be discarded.

**Stability and Storage**

Store lyophilized Cathflo Activase at refrigerated temperature (2–8°C/36–46°F). Do not use beyond the expiration date on the vial.

Protect the lyophilized material during extended storage from excessive exposure to light.

**HOW SUPPLIED**

Cathflo Activase (Alteplase) for injection is supplied as a sterile, lyophilized powder in 2 mg vials.

Cathflo®Activase® is available in a carton that contains one 2 mg vial of Cathflo® Activase® (Alteplase): NDC 50242-041-64 or a carton that contains ten 2 mg vials of Cathflo® Activase® (Alteplase): NDC 50242-041-10.
REFERENCES


Cathflo® Activase®
(Alteplase)
Manufactured by:

Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No. 1048

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