This reprint contains data from a Genentech-sponsored phase III clinical trial that led to the approval of Genentech's product Cathflo® Activase® (alteplase). The FDA has approved Cathflo® Activase® (alteplase) for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

This reprint contains information that is not contained in the approved product labeling, including history of catheter thrombolysis; rationale for the COOL-2 trial; additional information on materials, methods, and patients of the COOL-2 trial; and limitations of the COOL-2 trial.

Important Safety Information for Cathflo® Activase® (alteplase)

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retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility.

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 accompanying full Prescribing Information for additional important safety information.

Safety and Efficacy of Alteplase for Restoring Function in Occluded Central Venous Catheters: Results of the Cardiovascular Thrombolytic to Open Occluded Lines Trial

By Steven R. Deitcher, Mark R. Fesen, Paul M. Kiproff, Patricia A. Hill, Xin Li, Edward R. McCluskey, and Charles P. Semba for the Cardiovascular Thrombolytic to Open Occluded Lines–2 Investigators

Purpose: **To evaluate the safety and efficacy of alteplase (TPA) for restoring function to occluded central venous catheters (CVCs).**

Patients and Methods: **The study design was a phase III, open-label, single-arm multicenter trial. Subjects with occluded, nondialysis CVCs were enrolled. All subjects received a 2-mg dose of TPA within the dysfunctional catheter lumen that was allowed to dwell for 30 to 120 minutes. Functionality was tested at 30 and 120 minutes. If the CVC remained obstructed at 120 minutes, a second 2-mg TPA dose was allowed to dwell for 30 to 120 minutes. The primary safety end point was the rate of intracranial hemorrhage (ICH) within 5 days of treatment, and serious adverse events were recorded up to 30 days.**

Results: **Nine hundred ninety-five patients received treatment (female, 562; male, 433; mean age, 50.7 years; range, 2 to 91 years). CVCs treated were as follows: single (26%), double (39%), or triple (6%) lumen catheters or ports (29%). The primary end point was 0% ICH within 5 days. There were no cases of death, major bleeding episodes, or embolic events attributable to treatment. Flow was successfully restored in 52% and 78% of CVCs at 30 and 120 minutes after one dose, and 84% and 87% at 30 and 120 minutes after a second dose, respectively. Restoration of flow was 86%, 93%, 90%, and 79%, for single, double, and triple lumen catheters and ports, respectively. Estimated 30-day catheter patency was 74%.**

Conclusion: **A regimen of up to two 2-mg doses of TPA is safe and effective for the restoration of flow to occluded central venous catheters.**

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CENTRAL VENOUS catheters (CVCs) have become increasingly essential in the management of patients undergoing complex and intensive therapies, especially in the field of oncology. CVCs facilitate the consistent and timely infusion of antineoplastic agents, antimicrobial agents, blood products, and total parenteral nutrition as well the acquisition of blood samples for testing. Despite advances in device design and insertion techniques, the catheter lumens remain prone to occlusion. Catheter occlusion can result in treatment delay, surgical replacement, patient discomfort, and increased cost of care. Estimates suggest that 25% of CVCs become occluded, with thrombosis as the most common etiology.[1-3] Before 1999, the only approved pharmacologic agent for the medical treatment of thrombosed venous catheters was urokinase (Abbokinase-OpenCath, 5000 U; Abbott Laboratories, Abbott Park, IL) derived from human neonatal kidney cells. In January 1999, the Food and Drug Administration (FDA) suspended the distribution of urokinase because of the theoretical concern for the transmission of infectious agents.[4,5] Streptokinase has been used as a potential replacement; however, it is not FDA-approved for catheter clearance. In December 1999, the manufacturer of streptokinase (SK) (Streptase; AstraZeneca, Wayne, PA) issued warnings regarding the risk of life-threatening anaphylaxis when SK is used for treating occluded catheters.[6] Currently there are no approved alternatives to urokinase available in the United States for treating occluded venous catheters.

Alteplase (tissue plasminogen activator [TPA]) has been shown to be effective in the restoration of function to CVCs. In 1994, Haire et al[1] performed a double-blind, prospective, randomized trial of urokinase versus TPA (Genentech, Inc, San Francisco, CA) in dysfunctional catheters radiographically proven to be occluded by thrombus. Catheters were treated with 2 mg of TPA or 10,000 U of urokinase that was allowed to dwell in the device for 2 hours. After up to two treatments, TPA restored function in more catheters than urokinase (89% *v* 59%; $P = .013$). No treatment-related serious adverse events were reported during the serial delivery of up to two doses of either drug. Limitations of the study included the requirement of an interventional radiologist to inject the catheter in question with contrast and radiographically confirm the presence of clot at the catheter tip. Furthermore, the rate of spontaneous clearance remained unknown because there was no comparison to placebo.

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In July 1999, two pivotal FDA label-enabling phase III trials were initiated to determine the efficacy and safety of using up to two sequential 2-mg doses of TPA as an alternative to urokinase for CVC function restoration. The studies were designed to confirm the experience reported by Haire et al[1] but without the need for x-ray contrast-injections of the affected catheter. The Cardiovascular thrombolytic to Open Occluded Lines (COOL)-1 was a double-blind, placebo-controlled, prospective randomized trial to primarily evaluate the efficacy of TPA.[7,8] The end point was restoration of flow after administration of study drug (placebo or TPA). Function was restored in 74% of catheters treated with one dose of TPA versus 17% treated with placebo ($P < .0001$). Cumulative efficacy after up to two 2-mg doses of TPA was 90%. Although no significant adverse events were reported in COOL-1, the total study population was only 150 patients. To better evaluate the safety of TPA treatments, a larger single-arm, open-label multicenter trial was designed. The purpose of this report is to present the safety and efficacy results of the phase III COOL-2 trial that used TPA to treat dysfunctional central venous access devices in nearly 1,000 patients and present the largest, to our knowledge, reported study of patients undergoing thrombolytic treatment of CVCs.

PATIENTS AND METHODS

Objectives

The primary objective of the study was to evaluate the safety of serial administration of up to two intraluminal doses of TPA (2 mg and 2 mL) in restoring function in occluded CVCs. The secondary objectives were (1) to estimate the success rates at 30 and 120 minutes after administration of up to two doses of TPA and (2) to estimate the 30-day primary patency rate of catheters successfully treated with TPA on the first 450 patients enrolled.

Study Design

This was a phase III, open-label, single-arm, multicenter study conducted at 78 sites in the United States from November 1999 to December 2000. The trial was designed to enroll 1,000 patients with dysfunctional, indwelling, long-term CVCs (Fig 1) in a predominantly oncology population. The study protocol underwent approval of the investigational review board at each site, and all patients were provided informed consent before enrollment. Genentech, Inc, sponsored this phase III clinical trial.

Inclusion criteria. Subjects were eligible if they were hemodynamically stable and had a dysfunctional long-term CVC. All types of catheters were included except any catheter used for hemodialysis. Catheters with valves (eg, Groshong catheter; Bard Vascular Access, Salt Lake City, UT), peripherally inserted central catheters (PICCs), apheresis catheters, and chest/arm ports were allowed. Catheter dysfunction was defined as the inability to withdraw 3 mL of blood from the device. If multiple lumens were occluded, investigators were allowed to choose and treat only one lumen for the study.

Exclusion criteria. Subjects who met one or more of the following were excluded from participation: inability to infuse fluid volume necessary to fill catheter lumen with TPA, ability to successfully withdraw blood after repositioning patient, devices inserted less than 48 hours before enrollment, any evidence of mechanical or nonthrombotic occlusion, age less than 2 years, body weight of less than 10 kg, previously enrolled onto study, administration of any fibrinolytic agent within 24 hours of enrollment, known right-to-left shunt, patent foramen ovale, or atrial/ventricular septal defect. Subjects who were considered by the investigator to be at a high risk for bleeding events, embolic complications (eg, recent deep vein thrombosis or pulmonary embolism), or had a known condition for which bleeding constituted a significant hazard were also excluded.

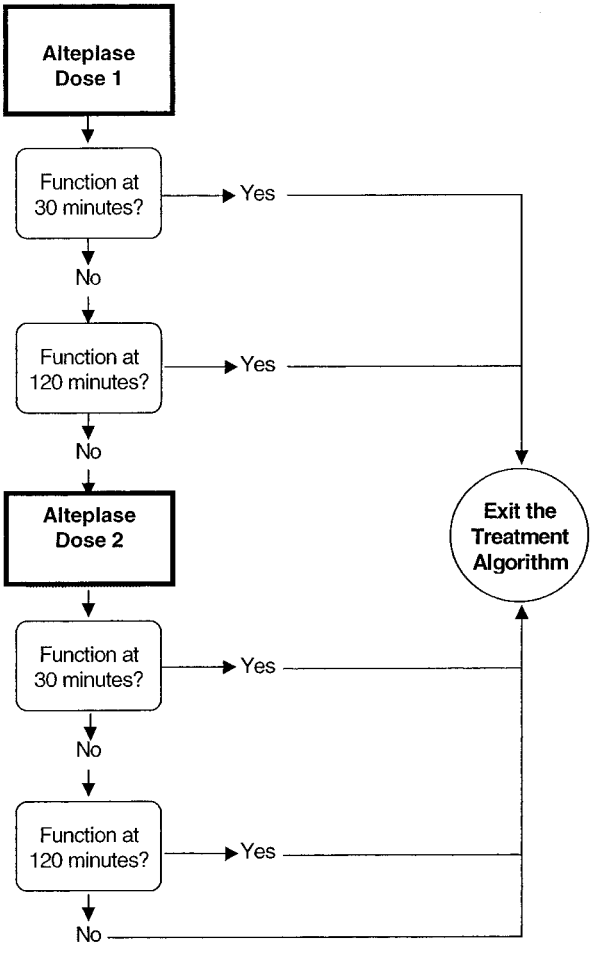

Fig 1. Treatment algorithm.

TPA is commercially manufactured in the United States in 50-mg and 100-mg vials. At each site, the 50-mg vial of lyophilized TPA powder (Activase; Genentech, Inc) was reconstituted with 50 mL of sterile water for injection (United States Pharmacopeia, Rockville, MD) to obtain a final concentration of 1 mg/mL. Using an aseptic technique, the pharmacist aliquotted 2-mL volumes of TPA into 10 mL sterile plastic syringes, which were kept frozen at −20°C until needed for the study. The preservation of bioactivity of reconstituted, frozen TPA is stable for at least 6 months and has been documented previously (data on file, Genentech, Inc, San Francisco, CA).[9,10] During the study, the frozen syringes were gently thawed at room temperature and used

immediately. The final concentration used was 1 mg/mL, and the intraluminal volume administered was 2 mL per dose, unless the patient had low body weight (< 30 kg). Subjects weighing ≥ 30 kg received a 2-mL intraluminal dose of TPA; subjects weighing ≥ 10 kg and less than 30 kg received intraluminal doses equal to 110% of the internal volume of the catheter lumen (not exceeding 2 mL).

All subjects received an intraluminal dose of TPA that was allowed to dwell in the catheter for 30 minutes (± 10 minutes). CVC function was assessed by first attempting to aspirate 3 mL of blood and, if successful, attempting infusion of 5 mL normal saline. For CVCs that remained dysfunctional after 30 minutes, the drug was allowed to remain in the device an additional 90 minutes, for a total of 120 minutes (± 10 minutes) after TPA administration. A second assessment of function was repeated. CVCs that remained dysfunctional after a single dose of TPA were treated with a second dose. Assessment of catheter function was again performed at 30 minutes (± 10 minutes) after administration of the second dose. If function was not restored, another assessment was made at 120 minutes (± 10 minutes).

Subjects exited the treatment algorithm when catheter function was restored or after assessment of CVC function after the second dose's 120-minute dwell time, whichever occurred first. For catheters successfully treated, the catheter was locked with heparin or saline solutions per routine care.

The safety evaluation had two components. First, serious adverse events were elicited from all subjects by telephone or in person at 5 days (± 1 day) after completion of the treatment algorithm. Serious adverse events of specific interest included intracranial hemorrhage (ICH), major hemorrhages, and embolic events. The second component was the collection of spontaneous serious adverse events confirmed by the investigators during the 30-day posttreatment period.

Outcome Variables

The primary safety outcome variable was the incidence of intracranial hemorrhage documented by computerized tomography within 5 days after completion of the treatment algorithm. The secondary safety outcome variables were as follows: (1) incidence of major hemorrhage (defined as severe blood loss [> 5 mL/kg] or blood loss requiring transfusion or causing hypotension) within 5 days of treatment, (2) embolic events (any serious embolic event, including pulmonary, arterial [eg, stroke, peripheral, or major organ], or cholesterol plaque) within 5 days of treatment, and (3) incidence of serious adverse events within 30 days of treatment.

The primary efficacy outcome variable was the overall rate of CVC function after serial administration of up to two intraluminal doses of TPA. Restored function was defined as the ability to withdraw 3 mL of blood from the CVC and infuse 5 mL of normal saline. Secondary efficacy outcome variable was the rate of restored catheter function at the end of 30 and 120 minutes after the first and second TPA dose and primary patency rate of successfully treated devices at 30 days for the first 450 patients enrolled.

Statistical Analysis

Safety. For the primary safety outcome measures, the proportion of subjects with an ICH within 5 days were used to estimate the event rate. Asymmetric confidence intervals (CIs) were also reported. For the secondary safety outcome measures (major hemorrhage and embolic events within 5 days), 95% Cis, using asymmetric CIs for small proportions, were determined. Safety was also assessed using reported narrative summaries of all serious adverse events up to 30 days after treatment.

Efficacy. For the primary efficacy outcome measure, the proportion of subjects with restored CVC function and 95% CIs after up to two doses of TPA were determined. For the secondary efficacy outcome measure, the proportion and 95% CIs of subjects with restored CVC function at 30 and 120 minutes after up to two doses of TPA were determined. For the 450 patients who had 30-day assessments of catheter patency, time to reocclusion was calculated using Kaplan-Meier analysis.

RESULTS

A total of 1,000 subjects were registered onto the study; however, three subjects were enrolled twice because of reocclusion, and, therefore, the actual number of subjects enrolled was 997. All subjects were scheduled to receive TPA; however, two patients had spontaneous return of catheter function and were not administered the study drug. A total of 995 subjects were treated with TPA and constitute the study population. The baseline characteristics of the study population are summarized in Table 1. The majority of subjects were female (56.5%) and white (78.6%). The overall mean age was 50.7 years (range, 2 to 91 years), and mean weight was 73.7 kg (range, 11.1 to 220.0 kg). The most common CVC treated was a double lumen external catheter (39.4%). Among the 997 subjects enrolled, 85 (8.5%) did not complete the 30-day study period. Table 2 summarizes the reasons for study discontinuation.

Safety Outcomes

A summary of adverse events is presented in Table 3. For the primary end point, there were no subjects who experienced an ICH during the study (95% CI, 0.0% to 0.4%). For the secondary end points, there were three cases of major hemorrhage (0.3%; 95% CI, 0.1% to 0.9%), and no subjects experienced an embolic event (95% CI, 0.0%, 0.4%) within 5 days after treatment. There was no correlation between adverse events and total TPA dose (2 mg *v* 4 mg), catheter-type, age, sex, or body weight. Of the major hemorrhages, two were experienced by oncology patients (one undergoing stem-cell transplant for Ewing's sarcoma 2 days after treatment and one undergoing chemotherapy for metastatic seminoma and subsequent Mallory-Weiss tear 2 days after treatment) who experienced hematemesis. One additional patient with an active flare of ulcerative colitis had an episode of hematochezia 3 days after treatment. None of the major bleeding incidences were interpreted by the investigator as related to TPA treatment.

Two subjects withdrew from the study as a result of serious adverse events (sepsis). Subject A, who had multiple myeloma, experienced fever and hypotension fifteen minutes after the administration of TPA. Peripheral-blood cultures were subsequently positive for *Acinetobacter baumanii* and *Acinetobacter haemolyticus*. The patient was treated with intravenous antibiotics and recovered. Subject B, who had renal cell carcinoma, recurrent fevers, and suspected catheter infection, experienced

Table 1. Selected Demographic and Baseline Characteristics

	Weight < 30 kg (n = 60)		Weight ≥ 30 kg (n = 935)		Total (n = 995)	
	No.	%	No.	%	No.	%
Sex						
Female	24	40.0	538	57.5	562	56.5
Male	36	60.0	397	42.5	433	43.5
Race						
White	42	70.0	740	79.1	782	78.6
Black	11	18.3	115	12.3	126	12.7
Asian/Pacific Islander	—		7	0.7	7	0.7
Hispanic	6	10.0	58	6.2	64	6.4
American Indian/Alaskan native	—		4	0.4	4	0.4
Other	1	1.7	11	1.2	12	1.2
Age, years						
Mean	5.0		53.6		50.7	
SD	2.56		17.92		20.88	
Weight, kg						
Mean	19.7		77.2		73.7	
SD	5.08		22.94		26.15	
CVC type						
Single	13	21.7	242	25.9	255	25.6
Double	20	33.3	372	39.8	392	39.4
Triple	4	6.7	56	6.0	60	6.0
Port	23	38.3	265	28.3	288	28.9
Time from catheter insertion to treatment, days						
Median	90.5		38.0		40.0	
Range	2-2457		0-3722		0-3722	
Time from dysfunction to treatment						
Median, days	0.0		0.0		0.0	
Range, days	0-99		0-963		0-963	
0 days	44/60	73.3	591/914	64.7	635/974	65.2
−14 to −1 days	14/60	23.3	272/914	29.8	286/974	29.4
< −14 days	2/60	3.3	51/914	5.6	53/974	5.4
Time from last known function to treatment, days						
Median	5.0		5.0		5.0	
Range	0-103		0-1,043		0-1,043	

dyspnea that required intensive care unit monitoring 7 hours after administration of TPA. Because the catheter was suspected as the source of infection, the device was removed. Catheter blood cultures were unobtainable because the catheter was occluded; however, a culture of the catheter tip was positive for *Staphylococcus epidermidis*. A ventilation-perfusion lung scan was normal.

Three subjects (0.3%) experienced adverse events that were considered possibly related to TPA therapy, including subject A, described above. Subject C, who had a history of a septic knee joint, experienced an episode of fever 8 hours after successful treatment of an occluded PICC line, and subject D, who had carcinomatosis from small-cell cancer of the lung, developed a septic episode 7 hours after successful treatment of an occluded catheter.

A total of 24 patients (2.4%) died during the 30-day study period, all within the ≥ 30-kg weight strata. No subjects died on the day of treatment, but five (0.5%) died within 5 days of treatment. None of the deaths were considered by the investigator to be related to TPA. All of the subjects had advanced malignancies and/or multiorgan failure.

Efficacy Outcomes

A cumulative summary of the efficacy is presented in Table 4. The primary efficacy outcome (ability to withdraw 3 mL of blood and infuse 5 mL of saline) was defined as the overall rate of restored catheter function after up to two doses of TPA. The proportion of subjects who experienced successful treatment was 87.2% (844 of 968; 95% CI, 84.9% to 89.2%).

Twenty-seven patients did not have complete catheter assessments (both withdrawal and infusion) at the end of treatment and were excluded from the primary analysis. Thirteen (48.1%) of 27 patients were administered infusion function at baseline. After withdrawal function was re-established, infusion function was not reassessed. If these

Table 2. Subject Discontinuations

	Weight < 30 kg (n = 60)		Weight ≥ 30 kg (n = 937)		Total (n = 997)	
	No.	%	No.	%	No.	%
Discontinued	2	3.3	83	8.9	85	8.5
Reason						
Death	—		19	22.9	19	22.4
Lost to follow-up	1/2	50.0	21	25.3	22	25.9
Physician's decision	—		20	24.1	20	23.5
Subject's/guardian's decision	1/2	50.0	21	25.3	22	25.9
Serious adverse event	—		2	2.4	2	2.4

13 subjects were included in the analysis and catheter function considered fully restored, the success rate would be 87.4% (857 of 981). The remaining 14 subjects did not have catheter assessments for the following reasons: the subject or physician decided that the subject could not wait for the assessment, the nurse involved was not aware of the study, or the PICC line was broken and, thus, no assessment could be made. If these 14 subjects were included in the analysis and it was assumed that the treatment failed, the overall success rate would be 85.9% (844 of 982).

The cumulative efficacy at 30 and 120 minutes after the first and second dose of TPA was 52.1%, 76.5%, 83.6%, and 87.2%, respectively (Table 5). Efficacy by catheter type after up to two doses of TPA was 86.2%, 93.3%, 89.7%, and

Table 3. Serious Adverse Events Within 30 Days of Treatment

	Weight < 30 kg (n = 60)		Weight ≥ 30 kg (n = 935)		Total (n = 995)	
	No.	%	No.	%	No.	%
Overall	1	1.7	28	3.0	29†	2.9
Body as a whole						
Carcinoma	—		10	1.1	10	1.0
Chest pain	—		1	0.1	1	0.2
Fever	—		1	0.2	1	0.2
Infection	—		3	0.3	3	0.3
Sepsis	—		4	0.3	4	0.4
Cardiovascular system	—		6	0.6	6	0.6
Deep thrombophlebitis	—		2	0.2	2	0.2
Myocardial infarct	—		1	0.1	1	0.1
Tachycardia	—		1	0.1	1	0.1
Thrombosis	—		1	0.1	1	0.1
Vascular disorder	—		1	0.1	1	0.1
Digestive system	—		6*	0.6	6	0.6
Gastrointestinal hemorrhage	—		1	0.1	1	0.1
Hematemesis	—		2	0.2	2	0.2
Nausea	—		2	0.2	2	0.2
Veno-occlusive liver disease	—		1	0.1	1	0.1
Vomiting	—		2	0.2	2	0.2
Hemic and lymphatic system	—		2	0.2	2	0.2
Hemolytic anemia	—		1	0.1	1	0.1
Thrombotic thrombocytopenic purpura	—		1	0.1	1	0.1
Metabolic and nutrition disorders	—		1	0.1	1	0.1
Dehydration	—		1	0.1	1	0.1
Respiratory system	—		1	0.1	1	0.1
Pneumonia	—		1	0.1	1	0.1
Skin and appendages	—		2	0.2	2	0.2
Herpes zoster	—		2	0.2	2	0.2
Urogenital system	1	1.7	1	0.1	2	0.4
Abnormal kidney function	1	1.7			1	0.1
Urinary tract infection	—		1	0.1	1	0.1

*Two patients each experienced two events (nausea and vomiting).

†One patient experienced two events (pneumonia and herpes zorter).

Table 4. Cumulative Restoration of Catheter Function at the End of Treatment by Subgroup

	120 Minutes			
	%	No.	Total in Subgroup	95% CI (%)
Overall	87.2	844	968	84.9-89.2
Age				
2-11 years	87.7	71	81	78.5-93.9
12-17 years	87.9	29	33	71.8-96.6
18-65 years	87.0	522	600	84.0-89.6
> 65 years	87.4	222	254	82.7-91.2
Sex				
Female	86.5	474	548	83.3-89.2
Male	88.1	370	420	84.6-91.0
CVC type				
Single	86.2	213	247	81.3-90.3
Double	93.3	361	387	90.3-95.6
Triple	89.7	52	58	78.8-96.1
Port	79.0	218	276	73.7-83.6
Duration of dysfunction to treatment				
0 days	90.6	557	615	88.0-92.8
−14 to −1 days	84.1	238	283	79.3-88.2
< −14 days	77.6	38	49	63.4-88.2
Unknown	52.4	11	21	29.8-74.3

79.0% for single, double, and triple lumen catheters and ports, respectively. The majority of devices were cuffed, tunneled catheters or ports (76%; 755 of 995). PICC lines have become increasingly popular as a less invasive, simpler alternative to tunneled devices and were eligible for the trial. Of the 240 PICC lines treated, the efficacy at 30 and 120 minutes after the first and second dose of TPA was 59.4%, 81.1%, 89.1%, and 92.9%, respectively.

CVC function was restored at the end of treatment for 844 of the 995 treated subjects; 385 of these subjects were from the subset of 450 who were to have an assessment of CVC function 30 days after treatment. Among the 385 subjects, data were available from 346 regarding catheter patency at 30 days (39 subjects were lost to follow-up at 30 days). Catheter reocclusion had occurred in 26.3% (91 subjects), for a 30-day patency rate of 73.7%. A Kaplan-

Table 5. Cumulative Catheter Function Restoration

	Weight < 30 kg (n = 60)	Weight ≥ 30 kg (n = 935)	Total Overall (n = 995)
First dose			
After 30 minutes			
%	55.9	51.8	52.1
No.	33	483	516
Total patients	59	932	991
95% CI	42.4% to 68.8%	48.6% to 55.1%	48.9% to 55.2%
After 120 minutes			
%	79.3	76.4	76.5
No.	46	701	747
Total patients	58	918	976
95% CI	66.6% to 88.8%	73.5% to 79.1%	73.7% to 79.2%
Second dose			
After 30 minutes			
%	84.7	83.6	83.6
No.	50	767	817
Total patients	59	918	977
95% CI	73.0% to 92.8%	81.0% to 85.9%	81.2% to 85.9%
After 120 minutes			
%	89.5	87.0	87.2
No.	51	793	844
Total patients	57	911	968
95% CI	78.5% to 96.0%	84.7% to 89.2%	84.9% to 89.2%

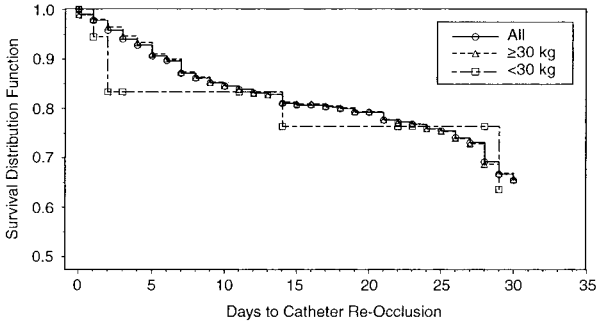

Fig 2. Kaplan-Meier curve for time to catheter reocclusion for the subset of 450 subjects.

Meier survival analysis was plotted using a worst-case assumption that the 39 subjects had occluded devices, for a 30-day patency rate of 65% **(**Fig 2).

DISCUSSION

Central venous catheters have greatly improved the ability to provide medical therapy for patients who require long-term parenteral therapy. Despite the advances in catheter technology and improvements in catheter care, device failure remains a commonplace conundrum, especially for the intravenous therapy team.[11-14] Not only is CVC occlusion a significant source of frustration for the caregiver and patient that delays needed therapy, it exposes the patient to additional risks arising from surgical revision, removal, and/or device replacement. Urokinase had been the established standard of care in troubleshooting venous access devices when simple saline or heparin flushes were unsuccessful. Though TPA has been shown to be a superior alternative to urokinase,[1] TPA had never been studied in large-scale pivotal trials. Although the COOL-1 study robustly established the efficacy of TPA therapy in catheter clearance, a larger phase III experience was required to assess the overall safety profile of using up to two 2-mg intraluminal doses of TPA. The COOL-2 trial was performed to principally assess the safety of the procedure and represents one of the largest thrombolytic trials for the management of CVC dysfunction.

The primary safety objective was the rate of intracranial hemorrhage within 5 days of treatment. There were no ICHs, embolic events, or study drug-related major hemorrhages or deaths. All of the serious adverse events that were reported were judged by the investigator to be related to the underlying disease with the exception of one event (fever). Two events of sepsis were judged by the investigator to be not related to study drug but were upgraded to possibly related by the trial sponsor. Because of the potential for TPA to liberate infected thrombotic material into the bloodstream, caution is warranted in the attempt to treat devices with suspected intraluminal infections. Our results also support the safety findings of both COOL-1 and Haire et al,[1] showing no treatment-related adverse bleeding events or evidence of systemic fibrinolysis. In Haire et al,[1] the mean pretreatment and posttreatment fibrinogen levels for patients treated with TPA was 392 mg/100 mL, and 385 mg/100 mL, respectively (not significant). Though many oncology patients have thrombocytopenia and are at increased risk for bleeding, studies evaluating the safety of TPA treatment in severely thrombocytopenic and/or neutropenic populations will require further investigation. Overall, the COOL-2 safety results were consistent with previous published studies and demonstrate a high margin of safety with no evidence of systemic fibrinolytic complications.

The primary efficacy outcome measure of the trial was the rate of restoration of CVC function after up to two boluses of 2 mg/2 mL TPA. On the basis of the estimate of efficacy in restoring function to thrombotically occluded catheters (89%, based on Haire et al[1]) and the prediction that 64% of catheters were thrombotically occluded, an efficacy rate of 57% after two treatments of TPA was expected.[1] The overall rate of CVC restoration in the current trial was 87.2%. This value is consistent with the predicted estimate if it is assumed that the investigators were highly effective in excluding mechanically occluded catheters (kinked devices or occlusions caused by nonthrombotic material) solely on the basis of clinical, bedside assessment of the device. TPA efficacy was high, regardless of catheter type, patient age, sex, race, or body weight. Efficacy seems to be related to duration of catheter dysfunction to treatment time. Catheters known to be occluded and treated more than 14 days after occlusion detection had a cumulative success rate of 77.6% (95% CI, 63.4% to 88.2.%), compared with 90.6% for devices treated on day 0 (95% CI, 88.0% to 92.8%).

The demographic and baseline characteristics of the subjects were consistent with those expected in a typical clinical setting where patients have significant underlying disease that necessitates implantation of a CVC. The distribution of catheter types was within the expected range.

Alteplase is the recombinantly derived analog of human TPA secreted from normal vascular endothelium and has higher fibrin specificity than urokinase (UK) and a shorter plasma half-life (UK, 16 minutes; TPA, 5 minutes). Currently, TPA is approved for acute myocardial infarction, acute ischemic stroke, and pulmonary embolism. The derivation of a 2-mg dose for catheter clearance was based on the analysis of Haire et al[1]. A single FDA-approved dose of urokinase for catheter clearance is 5,000 U. This is equal to 1.6% of the FDA-approved bolus dose of urokinase used for treating

pulmonary embolism in a 70-kg patient (4,400 U/kg). The approved dose of TPA for pulmonary embolism is 100 mg; therefore, Haire et al[1] empirically used 2-mg (rounded up to 2%) as the study dose for catheter clearance. Because TPA is reconstituted 1:1 with sterile water, the volume of a 2-mg dose is 2 mL. For the vast majority of normal, unobstructed CVCs, the intraluminal volume is usually between 1 to 2 mL. Therefore, a 2-mg configuration is feasible for most CVCs. With children in whom shorter devices were used, a dose equal to 110% of the catheter volume was used to minimize excess TPA delivery into the bloodstream.

Alternative agents to urokinase include TPA, SK, reteplase (Retavase; Centocor, Malvern, PA), and tenecteplase (TNKase; Genentech). Because of the potential for serious anaphylaxis, especially with repeated exposure, SK has not been considered a primary alternative to urokinase for catheter clearance.[6] Reteplase and tenecteplase are recombinantly derived variants of TPA and are approved for myocardial infarction; however, there are no peer-reviewed studies that describe their use for catheter clearance.

Low-dose warfarin has been demonstrated to reduce the rate of catheter-related venous thrombosis.[15,16] Assessment of catheter clearance using TPA in conjunction with known prophylactic warfarin was not evaluated in this study. Although the COOL-2 study population was predominantly composed of oncology patients, the percentage of patients on prophylactic warfarin was not recorded and warrants future investigation. Routine use of warfarin could potentially enhance 30-day catheter patency after TPA treatment.

With the unavailability of urokinase, many hospitals have resorted to using frozen aliquots of TPA; however, most outpatient facilities, such as skilled nursing facilities, free-standing clinics, or home infusion services, have not had access to frozen small-dose syringes because of a lack of access to freezers and/or a dedicated pharmacist. The COOL-2 trial used reconstituted and frozen syringes of TPA, and these results do not change the current constraints in the outpatient settings. However, the COOL trials are part of a phase III, FDA, label-enabling study that, if approved, would allow the availability of a 2-mg, single-use, patient-specific vial of TPA for use in catheter clearance and would obviate the need for aliquotting and freezing.

In conclusion, the results of the COOL-2 study have demonstrated that TPA, when administered at a dose of 2 mg/2 mL for up to two serial administrations and allowed to dwell up in the catheter for 30 to 120 minutes, is safe and effective for the restoration of catheter function in subjects with occluded central venous catheters.

APPENDIX

The appendix is available online at www.jco.org.

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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.

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Cathflo® Activase®
(Alteplase)

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