This reprint contains data from a Genentech-sponsored phase III clinical trial that led to the approval of Genentech's product Cathflo® Activase® (alteplase) for pediatric patients. 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 special considerations of maintaining CVADs in pediatric patients; history of catheter thrombolysis; rationale for the CAPS trial; additional information on materials, methods, and patients of the CAPS trial; and limitations of the CAPS trial.

The following author(s) of the attached publication are present or former employees of Genentech: Martha Blaney, Sarah Gray, Jennifer Armfield, and Charles P. Semba.

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retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.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

Alteplase for the Treatment of Central Venous Catheter Occlusion in Children: Results of a Prospective, Open-label, Single-arm Study (The Cathflo Activase Pediatric Study)

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PURPOSE: Alteplase is approved for use in the restoration of function to occluded central venous access devices (CVADs); however, there are few prospective studies in children. This study was undertaken to evaluate the safety and efficacy of alteplase in the treatment of CVAD occlusions in a pediatric population.

MATERIALS AND METHODS: A prospective, multicenter, open-label, single-arm study evaluating a maximum of two doses (≤2 mg per dose) of alteplase was performed in pediatric patients. Inclusion criteria included patient age less than 17 years with an occluded CVAD (single-, double-, and triple-lumen catheter or implanted port). Patients with hemodialysis catheters, those with known mechanical occlusion, or those considered at high risk for bleeding or embolization were excluded. Assessment of function was made 30 and 120 minutes (if required) after each dose. The primary objective of the study was to evaluate the safety of alteplase as measured by the incidence of intracranial hemorrhage (ICH); secondary objectives included the evaluation of specific targeted serious adverse events and efficacy of alteplase in the restoration of catheter function.

RESULTS: A total of 310 patients (174 male patients, 136 female patients; mean age, 7.2 years; range, 0.04–18.3 y) were treated; 55 of the patients (17.7%) were younger than 2 years of age. No patients experienced ICH (95% CI, 0%–1.2%). Nine serious adverse events were noted in eight patients (2.6% incidence), two of which were attributed by the investigator to study drug administration (one case of sepsis and one case of a ruptured catheter lumen). The cumulative rate of restoration of CVAD function after serial administration of a maximum of two instillations of alteplase, each with a maximum dwell time of 120 minutes, was 82.9% (95% CI, 78.2%–86.9%). Similar rates of catheter function restoration were seen among all catheter types studied; there were no clinically meaningful differences among age or sex subgroups.

CONCLUSION: The administration of alteplase is safe and effective for the restoration of function to CVADs in pediatric patients.

J Vasc Interv Radiol 2006; 17:1745–1751

Abbreviations: CAPS = Cathflo Activase Pediatric Study, COOL = Cardiovascular Thrombolytic to Open Occluded Lines [trial], CVAD = central venous access device, FDA = Food and Drug Administration, ICH = intracranial hemorrhage

THE preservation of central venous access devices (CVADs) in children remains a challenging medical management dilemma (1). CVAD care is distinctly different in children from that in adults; children tend to have fewer veins to select from, and the catheters have smaller bores with significantly smaller lumen volumes than do the catheters used in adults. Placement of the access devices often requires cooperative input from pediatricians/neonatologists, anesthesiologists, surgeons, interventionalists, nurses, and parents. Replacement or exchange of an occluded CVAD in a sick child can be a vexing issue resulting in interrup-

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DOI: 10.1097/01.RVI.0000241542.71063.83

tion of therapy, need for scheduled room time (operating room or angiography suite), repeat operative intervention, use of general anesthesia, and incremental health care costs to deal with delays and additional procedures. Therefore, the ability to noninvasively salvage the dysfunctional CVAD is critically important to minimize disruption in care and reduce the added risks of additional radiation exposure, anesthesia, and surgery.

Thrombolytic agents have been used during the past three decades as a potential method to restore flow to occluded CVADs in children; however, few prospective studies have been conducted to investigate prespecified techniques and endpoints (2–6). Before 1998, the only thrombolytic agent approved by the U.S. Food and Drug Administration (FDA) for catheter clearance was human-derived urokinase (Abbokinase Open-Cath; Abbott Laboratories, North Chicago, IL). However, the product was withdrawn from the market in November 1998 (7), and no approved product was available until 2001. In September 2001, the FDA approved the use of alteplase (Cathflo Activase; 2-mg/vial, Genentech, South San Francisco, CA) for the indication of restoring function to CVADs as assessed by the ability to withdraw blood (8). The approval was based on the pivotal phase III Cardiovascular Thrombolytic to Open Occluded Lines (COOL) trial (9) and COOL-2 trial (10), but the study population consisted predominantly of adult patients; patients younger than 2 years of age or with a body weight of less than 10 kg were excluded. Because of the scarcity of safety data in children, the FDA requested that an additional postmarketing study be conducted in pediatric patients (11). The Cathflo Activase Pediatric Study (CAPS) was conducted to specifically address the safety and efficacy of alteplase in a pediatric population with dysfunctional catheters.

MATERIALS AND METHODS

Objectives

The primary objective of the study was to evaluate safety, as measured by the incidence of intracranial hemorrhage (ICH) documented by computed tomography (CT) or magnetic resonance (MR) imaging, during the treatment period and within 48 hours after the completion of treatment with alteplase. Two prespecified populations were patients 2–16 years of age and those younger than 2 years of age. The secondary objectives were to estimate the rate of restoration of function to dysfunctional CVADs 30 and 120 minutes after administration of a maximum of two instillations of alteplase and to determine the rate of serious adverse events that occurred within 48 hours of treatment. The serious adverse events studied included major hemorrhage (defined as severe blood loss [>5 mL/kg] or blood loss resulting in hypotension or requiring transfusion), thrombosis, embolic events (defined as any serious embolic event including pulmonary or arterial events [eg, stroke, peripheral, or major organ] or cholesterol plaque), sepsis, catheter-related complications, or any other serious adverse event.

Study Design

The study was a phase IV prospective, open-label, single-arm, multicenter trial conducted at 42 sites in the United States from April 2002 to May 2003 as a postmarketing study that was requested by the FDA and sponsored by Genentech. The request specified that the study consist of at least 250 patients 2–16 years of age and 50 patients younger than 2 years of age (10). The protocol was approved by the institutional review boards at each site, and written informed consent or assent was obtained by a parent, legal guardian, or patient.

Inclusion criteria.—Patients were eligible if they were in clinically stable condition, less than 17 years of age, and had occlusion, defined as withdrawal dysfunction, of a CVAD (includes up to a triple-lumen catheter and ports). For patients who weighed 10 kg or more, withdrawal dysfunction was defined as inability to withdraw 3 mL of blood from the CVAD; for patients who weighed less than 10 kg, withdrawal dysfunction was defined as inability to withdraw 1 mL of blood from the CVAD. If multiple lumens were dysfunctional, the investigator chose one lumen for the study and treated the same lumen with study drug throughout the study. The ability to infuse fluids into the lumen at the volume necessary to instill alteplase was also required.

Exclusion criteria.—Patients were excluded if CVAD function was restored after repositioning, the CVAD was inserted less than 48 hours before enrollment, the CVAD was implanted specifically for hemodialysis, there was evidence of mechanical or nonthrombotic occlusion as determined by the investigator, the patient was previously enrolled in the study, the patient was treated with any thrombolytic agent within 24 hours of enrollment, the patient was at high risk for bleeding events or embolic events (ie, recent pulmonary embolism, deep vein thrombosis, endarterectomy, clinically significant right-to-left shunt) in the opinion of the investigator or had a known condition for which bleeding constituted a significant hazard, or the patient had a known hypersensitivity to alteplase or a component of the formulation.

Treatment protocol.—Alteplase (Cathflo Activase; Genentech) was provided as a sterile vial of lyophilized powder with a concentration after reconstitution with sterile water of 1 mg/mL (7). Each vial contains 2.2 mg alteplase (which includes a 10% overfill), 77 mg of L-arginine, 0.2 mg of polysorbate 80, and phosphoric acid for pH adjustment. Patients weighing 30 kg or more were to receive 2-mL instillations (2 mg) of alteplase within the catheter lumen, and patients weighing less than 30 kg were to receive instillations of alteplase equal to 110% of the estimated internal lumen volume of the dysfunctional CVAD (dose rounded to the nearest 0.1 mL, not to exceed 2 mL). Although this was not specified in the protocol, the previous safety study of Cathflo Activase used 10-mL syringes for administration of study medication (10).

Enrolled patients were eligible for serial treatment with a maximum of two instilled doses of alteplase, each with a maximum dwell time of 120 minutes. Assessment of CVAD function occurred 30 minutes after administration of each dose. CVAD function was assessed by first attempting aspiration of blood and, if that was successful, attempting infusion of normal saline solution. Restored function was

defined as the ability to withdraw 3 mL blood and infuse 5 mL normal saline solution in patients weighing 10 kg or more or the ability to withdraw 1 mL blood and infuse 3 mL normal saline solution in patients weighing less than 10 kg. If function was not restored at 30 minutes, another assessment of function was made at 120 minutes. Patients exited the treatment algorithm when restoration of CVAD function was established or after assessment of CVAD function after the 120-minute dwell time for the second instillation, whichever occurred first.

Assessment of safety had two components. All serious adverse events were to be recorded during the treatment period. Additionally, all serious adverse events were to be elicited from all patients or patients' representatives by telephone or in person at 48 hours after completion of the treatment algorithm. The posttreatment contact for the assessment of safety events occurred 48–96 hours after completion of the treatment algorithm. An adverse event was defined as serious if it resulted in death, was life-threatening, required or prolonged inpatient hospitalization, was disabling, resulted in a congenital anomaly or birth defect, may have jeopardized the patient, or may have required medical or surgical intervention to prevent one of these outcomes. Targeted serious adverse events of specific interest included ICH, major hemorrhage, thrombosis, embolic events, sepsis, and catheter-related complications. Screening CT or MR imaging was not performed on patients to exclude an ICH during the treatment period and within 48 hours of treatment. Adverse events that were not serious were not to be recorded.

Statistical Analysis

Safety and efficacy analyses were based on all enrolled patients who received treatment with alteplase (defined as the safety-evaluable population). Treatment was recorded as having occurred in patients who received at least one complete or partial instillation of alteplase.

For the primary safety endpoint of ICH, for each of the secondary safety endpoints (major hemorrhage, thrombosis, embolic events, sepsis, and catheter-related complications), and for the endpoint of any other medically important event, the event rate was calculated and an exact 95% CI was provided. Event rates and corresponding exact 95% CIs were also calculated for the two subgroups of patients less than 2 years of age and 2 years of age or older.

For the primary efficacy endpoint (cumulative restoration rate of CVAD function after a maximum of two instillations of alteplase, each with a maximum dwell time of 120 minutes) and for each of the secondary and other efficacy endpoints (restoration rate at 30 minutes after the first instillation, cumulative restoration rate at 120 minutes after the first instillation, and cumulative restoration rate at 30 minutes after the second instillation), the restoration rate was calculated and an exact 95% CI was provided. The event rates and corresponding exact 95% CIs were also calculated for the two subgroups: patients younger than 2 years of age and those 2 years of age or older. Patients who did not complete the treatment algorithm were considered to have experienced treatment failure for purposes of the efficacy analyses.

All statistical analyses were performed with SAS software (version 8.2; SAS, Cary, NC). The exact 95% CIs were computed with use of the F distribution method provided by Collett (12).

RESULTS

Demographics

The study population consisted of 310 treated patients (56.1% male and 43.9% female), the majority of whom were white (70.3%), with a mean age of 7.2 years (range, 0.04–18.3 y) (**Table 1**). Fifty-five patients were younger than 2 years of age, and 255 were 2 years of age or older. The overall mean body weight was 30.3 kg (range, 2.2–107.0 kg); 39 patients (12.6%) weighed less than 10 kg.

The most frequent types of CVAD (in descending order) were a port (51.6%), a double-lumen catheter (30.0%), a single-lumen catheter (14.5%), and a triple-lumen catheter (3.9%). By age stratum, the most common type of CVAD in the younger age group was a double-lumen catheter (49.1%) and the most common type in the older age group was a port (59.2%). The primary indications for catheter placement were chemotherapy administration (69.0%), hydration and/or blood transfusion (56.5%), and antibiotic administration (44.5%).

At the time of study treatment, 55% of patients had catheters implanted for less than 90 days and 24.3% had the implanted device for more than 1 year. The majority of patients (81%) received treatment with study drug on the same day that catheter dysfunction was diagnosed.

All enrolled patients were to receive treatment with a maximum of two serially instilled doses of alteplase. Of the 310 enrolled and treated patients, 255 (82.3%) received one dose of alteplase and 55 (17.7%) received two doses. In addition, a total of 282 patients (91.0%) completed the study treatment algorithm and the posttreatment follow-up assessment.

Protocol Deviations

Of the 310 patients, the treatment of 44 (14.2%) involved one or more major protocol deviations. These consisted of CVAD insertion less than 48 hours before enrollment ($n = 2$), high risk for bleeding or embolic events ($n = 2$), age greater than 17 years ($n = 3$), incomplete treatment algorithm ($n = 25$), and incorrect dose ($n = 16$). Incorrect dose was defined as administration of a dose of alteplase that was more than 30% greater than the protocol-specified dose or less than 77% of the protocol-specified dose. Overall, the percentage of patients with major protocol deviations was roughly equivalent in the two age strata (14.5% among patients <2 years of age and 14.1% among patients ≥ 2 years of age). However, for the group of patients younger than 2 years of age, incorrect dosing was the most frequent protocol deviation (7.3%), whereas for the older patient group, incomplete treatment algorithm was the most frequent protocol deviation (9.0%).

Safety Outcomes

The primary safety outcome measure was the incidence of ICH documented by CT/MR imaging during the treatment period and 48–96 hours after completion of the treatment algorithm; however, patients did not un-

Table 1
Demographic Characteristics and Baseline Catheter Information

Characteristic	Age <2 y (n = 55)	Age ≥2 y (n = 255)	Total (N = 310)
Sex			
Male	32 (58.2)	142 (55.7)	174 (56.1)
Female	23 (41.8)	113 (44.3)	136 (43.9)
Race			
White	41 (74.5)	177 (69.4)	218 (70.3)
Black	7 (12.7)	28 (11.0)	35 (11.3)
Asian/Pacific Islander	1 (1.8)	8 (3.1)	9 (2.9)
Hispanic	5 (9.1)	40 (15.7)	45 (14.5)
Other	1 (1.8)	2 (0.8)	3 (1.0)
Mean age (range), y	0.9 (0.04–2.0)	8.6 (2.0–18.3)	7.2 (0.04–18.3)
Mean weight (range), kg	8.0 (2.2–15.2)	35.2 (9.7–107.0)	30.3 (2.2–107.0)
CVAD type			
Single-lumen	15 (27.3)	30 (11.8)	45 (14.5)
Double-lumen	27 (49.1)	66 (25.9)	93 (30.0)
Triple-lumen	4 (7.3)	8 (3.1)	12 (3.9)
Port	9 (16.4)	151 (59.2)	160 (51.6)
CVAD age (d)*			
0–89	46 (83.6)	124 (48.8)	170 (55.0)
90–179	3 (5.5)	21 (8.3)	24 (7.8)
180–364	5 (9.1)	35 (13.8)	40 (12.9)
≥365	1 (1.8)	74 (29.1)	75 (24.3)
Duration of CVAD dysfunction (d)†			
0	40 (72.7)	211 (82.7)	251 (81.0)
1–6	11 (20.0)	34 (13.3)	45 (14.5)
7–13	4 (7.3)	8 (3.1)	12 (3.9)
≥14	–	2 (0.8)	2 (0.6)
Range	0–10	0–84	0–84
Infusion ability‡	43 (78.2)	216 (84.7)	259 (83.5)

* Defined as the number of days from catheter insertion to treatment.
† Defined as the number of days from determination of catheter dysfunction to treatment.
‡ Defined as the ability to infuse 5 mL for subjects weighing ≥10 kg and 3 mL for subjects weighing <10 kg; presented as number and percentage of subjects with infusion ability.
Note.—Values in parentheses are percentages unless specified otherwise.

dergo routine screening CT or MR imaging. No patients experienced an ICH during the study (95% CI, 0%–1.2%).

The secondary safety outcome measures included the incidence of targeted serious adverse events (major hemorrhage, thrombosis, embolic event, sepsis, and catheter-related complications) that occurred any time during the treatment period or within 48–96 hours as determined clinically by the investigator after completion of the treatment algorithm. No cases of major hemorrhage, thrombosis, or embolic events were reported during the study (95% CI for each event, 0%–1.2%). No deaths occurred during the study or the 48- to 96-hour observation period.

Overall, three cases of sepsis were reported (1.0%; 95% CI, 0.2%–2.8%). All three cases were in patients who were at least 2 years of age and who had preexisting infection. The first case was in a 10-year-old patient being treated for Ewing sarcoma who presented with neutropenia, fever/chills, and positive blood culture for Gram-negative bacilli. The patient received alteplase 6 days after admission, and cultures performed on that day were reported to be positive 3 days later. The catheter was then removed, and a culture of the catheter tip revealed an identical organism. This case represented the only case of protocol-defined sepsis. The second case was in a 4-year-old patient with pre–B-cell acute lymphocytic leukemia admitted for fever, neutropenia, fungal sepsis, and renal compromise who had been treated unsuccessfully with alteplase on the day of admission and died of *Candida albicans* septicemia 15 days after study treatment. The third case was in a 13-year-old patient with osteogenic sarcoma in whom progressive bacterial sepsis developed, which was assessed by the investigator to be related to alteplase administration. The patient was admitted with fever and blood cultures positive for *Staphylococcus* species. One day after admission, the patient was treated with two doses of alteplase and experienced hypotension requiring pressor support for 2.5 hours after treatment.

Four patients experienced catheter-related complications (1.3%; 95% CI, 0.4%–3.3%): one patient in the younger age group (1.8%) and three patients in the older age group (1.2%). The first case involved the rupture of the catheter lumen when it was forcibly infused with 0.1 mL of study drug in a patient with a 2-year-old Broviac catheter; this event was assessed by the investigator as related to alteplase administration. For the remaining three cases, no additional details were provided by the reporting investigator.

In total, nine serious adverse events were reported in eight patients (2.6%), two of which were assessed by the investigator as related to alteplase administration (one case of sepsis and one case of a ruptured catheter lumen). These included the four cases mentioned previously and one case of each of the following: fever, tumor lysis syndrome, convulsions/seizures, anxiety attack, and cardiomyopathy.

Efficacy Outcomes

The primary efficacy outcome measure was the overall (ie, cumulative) rate of restoration of CVAD function after serial administration of a maximum of two instillations of alteplase, each followed by a maximum 120-minute dwell time. The overall rates of restoration of catheter function at 30 and 120 minutes were 53.5% and 75.2% and 80.3% and 82.9%, respectively, after the first and second doses. Outcomes were similar among all subgroups (sex, age, CVAD type, body weight) (**Table 2; Figure**).

Table 2
Cumulative Rate of Restoration Catheter Function Overall and by Subgroup

Subgroup	No. of Patients	First Instillation		Second Instillation	
		30 minute Dwell Time	120 minute Dwell Time	30 minute Dwell Time	120 minute Dwell Time
Overall	310	166 (53.5)	233 (75.2)	249 (80.3)	257 (82.9)
Age (y)					
<2	55	24 (43.6)	38 (69.1)	40 (72.7)	44 (80.0)
≥2 to <7	106	58 (54.7)	81 (76.4)	87 (82.1)	89 (84.0)
≥7 to <12	74	38 (51.4)	56 (75.7)	60 (81.1)	61 (82.4)
≥12	75	46 (61.3)	58 (77.3)	62 (82.7)	63 (84.0)
Sex					
Male	174	80 (46.0)	124 (71.3)	136 (78.2)	141 (81.0)
Female	136	86 (63.2)	109 (80.1)	113 (83.1)	116 (85.3)
Body weight (kg)					
<10	39	18 (46.2)	26 (66.7)	28 (71.8)	31 (79.5)
≥10 to <30	160	86 (53.8)	125 (78.1)	132 (82.5)	135 (84.4)
≥30	111	62 (55.9)	82 (73.9)	89 (80.2)	91 (82.0)
Catheter type*					
Single-lumen	45	27 (60.0)	33 (73.3)	37 (82.2)	37 (82.2)
Double-lumen	93	46 (49.5)	70 (75.3)	75 (80.6)	76 (81.7)
Triple-lumen	12	4 (33.3)	9 (75.0)	10 (83.3)	11 (91.7)
Port	160	89 (55.6)	121 (75.6)	127 (79.4)	133 (83.1)

Note.—Values presented are the number (percentage) of subjects in the subgroup with restored function at or before the specified time point.
* If multiple lumens were dysfunctional, the investigator chose one lumen for the study; in this case, restoration of function refers to one lumen only.

DISCUSSION

The management of dysfunctional vascular accesses in sick children can be frustrating and can use significant resources from multiple caregivers, ranging from the primary physician and nursing staff to surgeons, radiologists, anesthesiologists, and phlebotomy/infusion teams. Instillation of a thrombolytic agent has been used in pediatric practice as a noninvasive method to salvage occluded catheters, and numerous retrospective single-center reports have been published, but there are few multicenter, prospective data from larger clinical trials.

Alteplase has been approved by the FDA for the restoration of function to occluded CVADs on the basis of the phase III COOL trials involving 1,135 treated patients (9,10). A total of 126 patients (11%) were 2–16 years of age, and no study drug–related adverse events were reported in this age group. However, there was insufficient enrollment of pediatric patients to enable any firm conclusions to be drawn regarding relative efficacy in the pediatric or low-weight subgroups, relative efficacy related to catheter types used, or relative rates of adverse events (8).

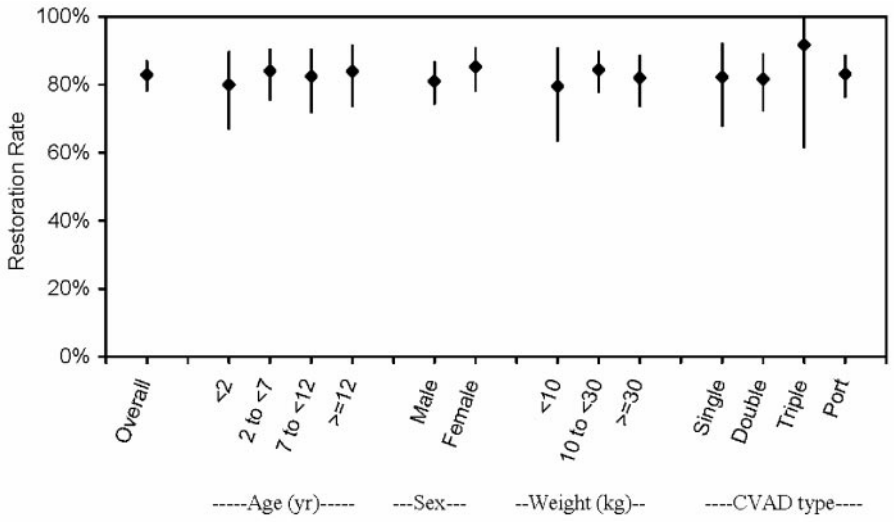

Figure. Cumulative rate of restoration of catheter function after a maximum of two doses of alteplase, overall and by subgroup. Diamond symbol represents observed catheter restoration rate after administration of a maximum of two instillations of alteplase, each with a maximum dwell time of 120 minutes; the vertical bars represent 95% CIs.

Catheter clearance with use of thrombolytic agents typically involves the instillation and filling of the entire dysfunctional catheter lumen with thrombolytic drug. In children, cathe-

ter lengths are variable and are customized by the implanting physician or nurse depending on the anatomy and size of the patient. The lumen volumes are often not precisely known. Instillation of alteplase in the CAPS trial involved slight overfilling of the estimated lumen volume (110%) in children weighing less than 30 kg and a 2-mg dose (2 mL) in all catheters in children weighing 30 kg or more. A small amount of alteplase may have been administered into the systemic circulation. When alteplase is administered according to the study protocol, any circulating plasma levels of alteplase are not expected to reach pharmacologic concentrations (13). The most frequent complication of systemic thrombolysis is bleeding, of which ICH represents the most severe adverse event. The main objective of the current study was to assess the overall safety of a maximum of two instilled doses of alteplase in children.

The results of this study showed that the treatment protocol is safe in children. No pediatric patient experienced ICH, major hemorrhage, thrombosis, or embolic event. In comparison with the COOL trials (9,10), the rates of serious adverse events were similar in pediatric and adult patients.

The most common serious adverse event reported in CAPS was sepsis (1%; $n = 3$). All these patients had evidence of infection before administration of alteplase. Alteplase or any thrombolytic agent should be used with caution in the presence of a known or suspected infection in the catheter. Because evaluation of the catheter involves instillation and flushing, the technique may release a localized infected clot or nonthrombotic debris into the systemic circulation.

The cumulative restoration rates observed in CAPS are similar to those observed in the COOL studies (9,10). The cumulative restoration rates reported in the COOL-2 study (10), which used an identical treatment regimen in 995 patients, were 52% and 75% at 30 and 120 minutes after one dose and 82% and 85% after a second dose, respectively. In this trial, the cumulative restoration rates were 54% and 75% at 30 and 120 minutes after one dose and 80% and 83% after a second dose, respectively. These findings are similar to those of a 2001 report in which alteplase was used to treat 228 children with 320 central venous catheter occlusions (6). In this study, patency was restored in 91% of catheters after one to three treatments. In the current study, the ability for alteplase to restore function was similar among all subgroups, including those based on age, body weight, and catheter type. Therefore, these factors do not appear to play a significant role in the restoration of patency to the occluded catheter.

The CAPS has certain limitations. Treatment of hemodialysis catheters was not evaluated, and therefore the study findings should not be translated to patients with occlusion of these devices. Bamgbola et al (14) have previously noted that low-dose, short-duration alteplase infusions were safe and effective for catheter thrombolysis in children with occluded hemodialysis catheters. In addition, the current study did not examine the use of alteplase for the simultaneous treatment of multiple catheter lumens. Future studies should assess the safety and efficacy of alteplase in patients with multiple-lumen catheter occlusion. In addition, use of shorter or longer alteplase dwell times, including "locking" the catheter with alteplase instead of heparin as a means for prophylactic maintenance of patency in troublesome devices, also was not evaluated (15). Although Weck et al (15) recently reported that 90% of thrombolytic activity was maintained 7 days after alteplase reconstitution with sterile water for injection, further evaluation is warranted before alteplase can be recommended as a locking solution. An incomplete treatment algorithm (caused by missed assessment or missed dose) occurred in 25 patients (8.1%), and incorrect dosing occurred in 16 patients (5.2%). Although these patients were included in the analysis, these results are unlikely to affect the overall efficacy, because an incomplete treatment algorithm would likely decrease the efficacy as underdosing would. Finally, another limitation of this study is that the volume of Cathflo Activase administered frequently exceeded that of the catheter lumen volume (especially in patients weighing <30 kg), which could have resulted in mechanical dislodgement of the catheter occlusion. However, because the efficacy was similar to that observed in the COOL-1 study (9), which was placebo controlled, this is unlikely to have affected the observed efficacy rates.

On the basis of the overall data submitted, the FDA reviewed and amended the prescribing information for Cathflo Activase to include this clinical study (8). In conclusion, the trial results support that the use of alteplase is safe and effective in the restoration of function to occluded CVADs in children and infants.

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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)

Manufactured by:
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A Member of the Roche Group
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94080-4990
US License No. 1048

FDA Approval Date January 2005
Revised: 02/2019