

Cathflo™ Activase® [Alteplase]

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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. Fermentation is carried out in a nutrient medium containing the antibiotic gentamicin sulfate, 100 mg/L. The presence of the antibiotic is not detectable in the final product.

Cathflo Activase 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.

26 **CLINICAL PHARMACOLOGY**

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

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

37 When Cathflo Activase is administered for restoration of function to
38 central venous access devices according to the instructions in [DOSAGE](#)
39 [AND ADMINISTRATION](#), circulating plasma levels of Alteplase are not
40 expected to reach pharmacologic concentrations. If a 2-mg dose of
41 Alteplase were administered by bolus injection directly into the systemic
42 circulation (rather than instilled into the catheter), the concentration of
43 circulating Alteplase would be expected to return to endogenous
44 circulating levels of 5–10 ng/mL within 30 minutes (1).

45 **CLINICAL STUDIES**

46 Two clinical studies were performed in patients with improperly
47 functioning central venous access devices (CVADs). A
48 placebo-controlled, double-blind, randomized trial (Trial 1) and a larger
49 open-label trial (Trial 2) investigated the use of Alteplase in patients who
50 had an indwelling CVAD for administration of chemotherapy, total
51 parenteral nutrition, or long-term administration of antibiotics or other
52 medications. Both studies enrolled patients whose catheters were not
53 functioning (defined as the inability to withdraw at least 3 cc of blood
54 from the device) but had the ability to instill the necessary volume of
55 study drug. Patients with hemodialysis catheters or a known mechanical
56 occlusion were excluded from both studies. Also excluded were patients

57 considered at high risk for bleeding or embolization (see PRECAUTIONS,
58 [Bleeding](#)), as well as patients who were younger than 2 years old or
59 weighed less than 10 kg. Restoration of function was assessed by
60 successful withdrawal of 3 cc of blood and infusion of 5 cc of saline
61 through the catheter.

62 Trial 1 tested the efficacy of a 2 mg/2 mL Alteplase dose in restoring
63 function to occluded catheters in 150 patients with catheter occlusion up to
64 24 hours in duration. Patients were randomized to receive either Alteplase
65 or placebo instilled into the lumen of the catheter, and catheter function
66 was assessed at 120 minutes. Restoration of function was assessed by
67 successful withdrawal of 3 cc of blood and infusion of 5 cc of saline
68 through the catheter. All patients whose catheters did not meet these
69 criteria were then administered Alteplase, until function was restored or
70 each patient had received up to two active doses. After the initial dose of
71 study agent, 51 (67%) of 76 patients randomized to Alteplase and 12
72 (16%) of 74 patients randomized to placebo had catheter function restored.
73 This resulted in a treatment-associated difference of 51% (95% CI is
74 37% to 64%). A total of 112 (88%) of 127 Alteplase-treated patients had
75 restored function after up to two doses.

76 Trial 2 was an open-label, single arm trial in 995 patients with catheter
77 dysfunction and included patients with occlusions present for any
78 duration. Patients were treated with Alteplase with up to two doses of
79 2 mg/2 mL (less for children who weighed less than 30 kg, see [DOSAGE](#)
80 [AND ADMINISTRATION](#)) instilled into the lumen of the catheter.
81 Assessment for restoration of function was made at 30 minutes after each
82 instillation. If function was not restored, catheter function was re-assessed
83 at 120 minutes. Thirty minutes after instillation of the first dose, 516
84 (52%) of 995 patients had restored catheter function. One hundred twenty
85 minutes after the instillation of the first dose, 747 (75%) of 995 patients
86 had restored catheter function. If function was not restored after the first
87 dose, a second dose was administered. Two hundred nine patients
88 received a second dose. Thirty minutes after instillation of the second

89 dose, 70 (33%) of 209 patients had restored catheter function. One
90 hundred twenty minutes after the instillation of the second dose, 97 (46%)
91 of 209 patients had restored catheter function. A total of 844 (85%) of
92 995 patients had function restored after up to 2 doses.

93 Similar rates of catheter function restoration were seen among all catheter
94 types studied (single-, double-, and triple-lumen, and implanted ports).

95 There were no gender differences observed in the rate of catheter function
96 restoration. Results were similar across age subgroups, but there was
97 insufficient enrollment of pediatric patients to draw any conclusions
98 regarding relative efficacy in pediatric patients (see PRECAUTIONS,
99 [Pediatric Use](#)).

100 Across both trials, 796 (68%) of 1043 patients with occlusions present for
101 less than 14 days had restored function after one dose, and 902 (88%) had
102 function restored after up to two doses. Of 53 patients with occlusions
103 present for longer than 14 days, 30 (57%) patients had function restored
104 after a single dose, and a total of 38 patients (72%) had restored function
105 after up to two doses.

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

109 **INDICATIONS AND USAGE**

110 Cathflo™ Activase® is indicated for the restoration of function to central
111 venous access devices as assessed by the ability to withdraw blood.

112 **CONTRAINDICATIONS**

113 Cathflo Activase should not be administered to patients with known
114 hyper-sensitivity to Alteplase or any component of the formulation
115 (see [DESCRIPTION](#)).

116 **WARNINGS**

117 None.

118 **PRECAUTIONS**

119 **General**

120 Catheter dysfunction may be caused by a variety of conditions other than
121 thrombus formation, such as catheter malposition, mechanical failure,
122 constriction by a suture, and lipid deposits or drug precipitates within the
123 catheter lumen. These types of conditions should be considered before
124 treatment with Cathflo Activase.

125 Because of the risk of damage to the vascular wall or collapse of
126 soft-walled catheters, vigorous suction should not be applied during
127 attempts to determine catheter occlusion.

128 Excessive pressure should be avoided when Cathflo Activase is instilled
129 into the catheter. Such force could cause rupture of the catheter or
130 expulsion of the clot into the circulation.

131 **Bleeding**

132 The most frequent adverse reaction associated with all thrombolytics in all
133 approved indications is bleeding (3,4). Cathflo Activase has not been
134 studied in patients known to be at risk for bleeding events that may be
135 associated with the use of thrombolytics. Caution should be exercised
136 with patients who have active internal bleeding or who have had any of
137 the following within 48 hours: surgery, obstetrical delivery, percutaneous
138 biopsy of viscera or deep tissues, or puncture of non-compressible vessels.
139 In addition, caution should be exercised with patients who have
140 thrombocytopenia, other hemostatic defects (including those secondary to
141 severe hepatic or renal disease), or any condition for which bleeding
142 constitutes a significant hazard or would be particularly difficult to
143 manage because of its location, or who are at high risk for embolic
144 complications (e.g., venous thrombosis in the region of the catheter).
145 Death and permanent disability have been reported in patients who have

146 experienced stroke and other serious bleeding episodes when receiving
147 pharmacologic doses of a thrombolytic.

148 Should serious bleeding in a critical location (e.g., intracranial,
149 gastrointestinal, retroperitoneal, pericardial) occur, treatment with
150 Cathflo Activase should be stopped and the drug should be withdrawn
151 from the catheter.

152 **Infections**

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

158 **Re-Administration**

159 In clinical trials, patients received up to two 2 mg/2 mL doses (4 mg total)
160 of Alteplase. Additional re-administration of Cathflo Activase has not
161 been studied. Antibody formation in patients receiving one or more doses
162 of Cathflo Activase for restoration of function to CVADs has not been
163 studied.

164 **Drug Interactions**

165 The interaction of Cathflo Activase with other drugs has not been formally
166 studied. Concomitant use of drugs affecting coagulation and/or platelet
167 function has not been studied.

168 **Drug/Laboratory Test Interactions**

169 Potential interactions between Cathflo Activase and laboratory tests have
170 not been studied.

171 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

172 Long-term studies in animals have not been performed to evaluate the
173 carcinogenic potential or the effect on fertility. Short-term studies that
174 evaluated tumorigenicity of Alteplase and effect on tumor metastases were

175 negative in rodents. Studies to determine mutagenicity (Ames test) and
176 chromosomal aberration assays in human lymphocytes were negative at all
177 concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic
178 index, was evidenced only after prolonged exposure at high concentrations
179 exceeding those expected to be achieved with Cathflo Activase.

180 **Pregnancy (Category C)**

181 Alteplase has been shown to have an embryocidal effect due to an
182 increased postimplantation loss rate in rabbits when administered
183 intravenously at doses approximately 100 times (3 mg/kg) the human dose
184 for restoration of function to occluded CVADs. No maternal or fetal
185 toxicity was evident at 33 times (1 mg/kg) the human dose for restoration
186 of function to occluded CVADs in pregnant rats and rabbits dosed during
187 the period of organogenesis.

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

191 **Nursing Mothers**

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

195 **Pediatric Use**

196 Cathflo Activase has not been studied in patients who are younger than
197 2 years of age or who weigh less than 10 kg. In Trials 1 and 2, 126 (11%)
198 of 1135 patients treated were from 2 to 16 years of age. No study
199 drug-related adverse events were observed in these patients. A total of
200 65 patients (6% of all patients treated in the studies) weighed ≥ 10 kg and
201 < 30 kg. These low body weight patients received up to two doses of
202 Alteplase, with each dose equal to 110% of the internal lumen volume of
203 the catheter (to a maximum dose of 2 mg). The rates of catheter function
204 restoration in these subsets of patients were similar to those observed in

205 adult patients. However, there was insufficient enrollment of pediatric
206 patients to draw any conclusions regarding relative efficacy in the
207 pediatric or low weight subgroups, relative efficacy related to catheter
208 types used in these patients, or relative rates of adverse events.

209 **Geriatric Use**

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

217 **ADVERSE REACTIONS**

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

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

225 The data described below reflect exposure to Cathflo Activase in
226 1122 patients, of whom 880 received a single dose and 242 received two
227 sequential doses of Cathflo Activase.

228 In the Cathflo Activase clinical trials, only limited, focused types of
229 serious adverse events were recorded, including death, major hemorrhage,
230 intracranial hemorrhage, pulmonary or arterial emboli, and other serious
231 adverse events not thought to be attributed to underlying disease or
232 concurrent illness. Major hemorrhage was defined as severe blood loss
233 (>5 mL/kg), blood loss requiring transfusion, or blood loss causing
234 hypotension. Non-serious adverse events and serious events thought to be

235 due to underlying disease or concurrent illness were not recorded. Patients
236 were observed for serious adverse events until catheter function was
237 deemed to be restored or for a maximum of 4 or 6 hours depending on
238 study. For most patients the observation period was 30 minutes to
239 2 hours. Spontaneously reported deaths and serious adverse events that
240 were not thought to be related to the patient's underlying disease were also
241 recorded during the 30 days following treatment.

242 Four catheter-related sepsis events occurred from 15 minutes to 1 day after
243 treatment with Alteplase, and a fifth sepsis event occurred on Day 3 after
244 Alteplase treatment. All 5 patients had positive catheter or peripheral
245 blood cultures within 24 hours after symptom onset.

246 Three patients had a major hemorrhage from a gastrointestinal source from
247 2 to 3 days after Alteplase treatment. One case of injection site
248 hemorrhage was observed at 4 hours after treatment in a patient with
249 pre-existing thrombocytopenia. These events may have been related to
250 underlying disease and treatments for malignancy, but a contribution to
251 occurrence of the events from Alteplase cannot be ruled out. There were
252 no reports of intracranial hemorrhage.

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

259 There were no gender-related differences observed in the rates of adverse
260 reactions. Adverse reactions profiles were similar across age subgroups,
261 but there was insufficient enrollment of pediatric patients to draw any
262 conclusions regarding relative adverse event rates (see PRECAUTIONS,
263 [Pediatric Use](#)).

264 **Allergic Reactions**

265 No allergic-type reactions were observed in the trials in patients treated
266 with Alteplase. If an anaphylactic reaction occurs, appropriate therapy
267 should be administered.

268 **DOSAGE AND ADMINISTRATION**

269 Cathflo Activase is for instillation into the dysfunctional catheter at a
270 concentration of 1 mg/mL.

- Patients weighing ≥ 30 kg: 2 mg in 2 mL
- Patients weighing ≥ 10 to < 30 kg: 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL

271

272 If catheter function is not restored at 120 minutes after 1 dose of
273 Cathflo Activase, a second dose may be instilled (see Instructions for
274 Administration). There is no efficacy or safety information on dosing in
275 excess of 2 mg per dose for this indication. Studies have not been
276 performed with administration of total doses greater than 4 mg
277 (two 2-mg doses).

278 **Instructions for Administration**

279 Preparation of Solution

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

- 281 1. Aseptically withdraw 2.2 mL of Sterile Water for Injection, USP
282 (diluent is not provided). Do not use Bacteriostatic Water for
283 Injection.
- 284 2. Inject the 2.2 mL of Sterile Water for Injection, USP, into the
285 Cathflo Activase vial, directing the diluent stream into the powder.
286 Slight foaming is not unusual; let the vial stand undisturbed to allow
287 large bubbles to dissipate.
- 288 3. Mix by gently swirling until the contents are completely dissolved.
289 Complete dissolution should occur within 3 minutes. **DO NOT**
290 **SHAKE**. The reconstituted preparation results in a colorless to pale
291 yellow transparent solution containing 1 mg/mL Cathflo Activase at a
292 pH of approximately 7.3.

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

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

299 Instillation of Solution into the Catheter

- 300 1. Inspect the product prior to administration for foreign matter and
301 discoloration.
- 302 2. Withdraw 2.0 mL (2.0 mg) of solution from the reconstituted vial.
- 303 3. Instill the appropriate dose of Cathflo Activase (see [DOSAGE AND](#)
304 [ADMINISTRATION](#)) into the occluded catheter.
- 305 4. After 30 minutes of dwell time, assess catheter function by attempting
306 to aspirate blood. If the catheter is functional, go to Step 7. If the
307 catheter is not functional, go to Step 5.
- 308 5. After 120 minutes of dwell time, assess catheter function by
309 attempting to aspirate blood and catheter contents. If the catheter is
310 functional, go to Step 7. If the catheter is not functional, go to Step 6.
- 311 6. If catheter function is not restored after one dose of Cathflo Activase,
312 a second dose may be instilled. Repeat the procedure beginning with
313 Step 1 under [Preparation of Solution](#).
- 314 7. If catheter function has been restored, aspirate 4–5 mL of blood to
315 remove Cathflo Activase and residual clot, and gently irrigate the
316 catheter with 0.9% Sodium Chloride, USP.

317 **Any unused solution should be discarded.**

318 **Stability and Storage**

319 Store lyophilized Cathflo Activase at refrigerated temperature
320 (2–8°C/36–46°F). Do not use beyond the expiration date on the vial.
321 Protect the lyophilized material during extended storage from excessive
322 exposure to light.

323 **HOW SUPPLIED**

324 Cathflo Activase is supplied as a sterile, lyophilized powder in 2-mg vials.

325 Each carton contains one 2-mg vial of Cathflo™ Activase®:
326 NDC 50242-041-63.

327 **REFERENCES**

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344