Administering Intravenous Alteplase
(Tissue Plasminogen Activator [tPA])

**Step 1:** Eligibility---The eligibility criteria for patients with acute ischemic stroke within 3 hours of symptom onset include:

- An adult (≥18 years of age)
- Exclusion of intracranial hemorrhage by an imaging technique sensitive for the presence of hemorrhage
- Arrives at the emergency department in time to be treated within 3 hours of symptom onset

**Step 2:** Review Contraindications & Additional warnings---See IV tPA Inclusion & Exclusion Criteria Worksheet (attached)

**Step 3:** Discuss treatment options, risks and benefits of IV tPA with patient and/or family

**Step 4:** Treat Eligible Patients

- The recommended dose of IV tPA is 0.9 mg/kg (not to exceed 90 mg total dose) infused over 60 minutes with 10% of the total dose administered as an initial bolus over 1 minute
- The goal for treatment of IV tPA is to give bolus and initiate infusion to eligible patient in less than 60 minutes of patient arrival

**Patient Monitoring During and Post tPA Therapy**

- See attached information regarding close observation and frequent monitoring of patients for neurologic changes, any signs/symptoms of intracranial hemorrhage, and any signs of adverse drug reactions are important during patient recovery.
For acute ischemic stroke

Activase (alteplase) dosing and administration

Dosing

The recommended dose of Activase is 0.9 mg/kg (not to exceed 90-mg total dose) infused over 60 minutes with 10% of the total dose administered as an initial intravenous (IV) bolus over 1 minute.

For information on reconstitution of 50- and 100-mg vials of Activase, see full Prescribing Information.

Administration of bolus

Step 1. Inspect solution
After reconstitution to 1 mg/mL, inspect solution for particulate matter and discoloration prior to administration.

Step 2. Discard excess
To ensure proper dosing, discard excess by removing from vial any quantity of drug in excess of that specified for patient treatment. When drawing out excess solution, be sure to insert the needle into the peripheral area of the vial top, away from the puncture site caused by the transfer device.

Step 3. Prepare bolus
Withdraw 10% of the 0.9 mg/kg dose in one of the following ways:
- Remove from vial using a syringe and needle,
- Remove from port (second injection site) on infusion line after infusion set is primed, or
- Program infusion pump to deliver bolus at infusion initiation. Remember to prime the IV pump with the Activase solution so that the remainder of the infusion begins immediately following the bolus dose

Step 4. Administer bolus
Administer initial IV bolus over 1 minute.

Administration of remainder of dose

Step 5. Administer remainder
Infuse the remaining 90% of the 0.9 mg/kg dose over 60 minutes.
- 100-mg vials—Spike the stopper of a reconstituted vial of Activase with an infusion set, using the same puncture site created by the transfer device.
- Peel the clear plastic hanger from the vial label. Hang the Activase vial—OR—Infuse the remaining 90% of the 0.9-mg/kg dose over 60 minutes.

No medication should be added to infusion solutions that contain Activase.

For specifics regarding dosing and administration, please see the Activase full Prescribing Information.

Indication

Activase (Alteplase) is indicated for the management of acute ischemic stroke in adults for improving neurological recovery and reducing the incidence of disability. Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of hemorrhage (see CONTRAINDICATIONS in the full prescribing information).

Important Safety Information

All thrombolytic agents increase the risk of bleeding, including intracranial bleeding, and should be used only in appropriate patients. Not all patients with acute ischemic stroke will be eligible for Activase therapy, including patients with evidence of recent or active bleeding; recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke; uncontrolled high blood pressure; or impaired blood clotting.

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

Close observation and frequent monitoring of patients for neurologic changes, any signs/symptoms of intracranial hemorrhage, and any signs of adverse drug reactions are important during patient recovery.

Consider using the Activase Therapy Checklist as a guide in tracking your patients’ recovery.

**During tPA therapy**
- **Perform neurologic assessment**
  - The use of a stroke rating scale, preferably the NIHSS, is recommended.
  - Repeat every 15 minutes during the 1-hour infusion to monitor for neurologic deterioration.
- **Check for major and/or minor bleeding**
  - All body secretions should be tested for occult blood.
  - Major bleeding: intracranial, retroperitoneal, gastrointestinal, or genitourinary hemorrhages.
  - Minor bleeding: gums, venipuncture sites, hematuria, hemaoptysis, skin hematomas, or ecchymosis.
  - Arterial and venous punctures should be minimized and checked frequently.
- **Monitor blood pressure**
  - Every 15 minutes during the 1-hour infusion.
  - Blood pressure should be monitored frequently and controlled during and after tPA administration (systolic blood pressure ≤ 185 mm Hg and diastolic blood pressure ≤ 110 mm Hg).
  - Administer antihypertensive medications to maintain blood pressure at or below these levels.
- **Discontinue infusion and obtain an emergency CT scan**
  - If the patient develops severe headache, acute hypertension, nausea, or vomiting; or has a worsening neurologic examination.
- **Monitor for signs of orolingual angioedema**
  - If angioedema is noted, promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids, or epinephrine) and consider discontinuing tPA infusion.

**Post tPA therapy**
- **Continue to monitor for neurologic deterioration**
  - Every 15 minutes for the first hour after the infusion is stopped.
  - Every 30 minutes for the next 6 hours.
  - Hourly from the eighth postinfusion hour until 24 hours after the infusion is stopped.
- **Continue to check for major and/or minor bleeding**
- **Continue to monitor and control blood pressure**
  - Every 15 minutes for the first hour after the infusion is stopped.
  - Every 30 minutes for the next 6 hours.
  - Hourly from the eighth postinfusion hour until 24 hours after the infusion is stopped.
- **Obtain a follow-up CT scan or MRI**
  - At 24 hours before starting anticoagulants or antiplatelet agents.
- **Continue to monitor for signs of orolingual angioedema**

If any complications occur, immediately inform the attending physician or neurologist.

---

**Activase is the standard of care for treating eligible acute ischemic stroke patients within 3 hours.**

Note: Each of these guidelines or policy statements represents only one possible approach to the treatment of eligible acute ischemic stroke patients. Each healthcare practitioner and institution will need to exercise professional judgment in creating or adopting treatment protocols or guidelines, as well as in the treatment of each individual patient.

- tPA = tissue plasminogen activator; NIHSS = National Institutes of Health Stroke Scale; CT = computerized tomography; MRI = magnetic resonance imaging.

---

**References:**

Please see Indication and Important Safety Information on next page.
### Activase (alteplase) Therapy Checklist\(^1,2\)

#### Perform neurologic assessments: unchanged (u); improving (i); deteriorating (d)

**Every 15 minutes for the first 2 hours after start of infusion**

<table>
<thead>
<tr>
<th>Minutes:</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>105</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic assessment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Every 30 minutes for the next 6 hours after infusion**

<table>
<thead>
<tr>
<th>Minutes:</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>270</th>
<th>300</th>
<th>330</th>
<th>360</th>
<th>390</th>
<th>420</th>
<th>450</th>
<th>480</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic assessment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hourly from the eighth postinfusion hour until 24 hours after infusion**

<table>
<thead>
<tr>
<th>Hours:</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic assessment:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Monitor blood pressure (BP)

**Every 15 minutes for the first 2 hours after start of infusion**

<table>
<thead>
<tr>
<th>Minutes:</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>105</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Every 30 minutes for the next 6 hours after infusion**

<table>
<thead>
<tr>
<th>Minutes:</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>270</th>
<th>300</th>
<th>330</th>
<th>360</th>
<th>390</th>
<th>420</th>
<th>450</th>
<th>480</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hourly from the eighth postinfusion hour until 24 hours after infusion**

<table>
<thead>
<tr>
<th>Hours:</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart time:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### Indication

Activase (Alteplase) is indicated for the management of acute ischemic stroke in adults for improving neurological recovery and reducing the incidence of disability. **Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of hemorrhage (see CONTRAINDICATIONS in the full prescribing information).**

### Important Safety Information

All thrombolytic agents increase the risk of bleeding, including intracranial bleeding, and should be used only in appropriate patients. Not all patients with acute ischemic stroke will be eligible for Activase therapy, including patients with evidence of recent or active bleeding; recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke; uncontrolled high blood pressure; or impaired blood clotting.

Please see full Prescribing Information for additional Important Safety Information.
20.6% for accelerated infusion of Alteplase, 21.5% for SK (IV), and 22.0% for SK (SQ). An angiographic substudy of the GUSTO trial provided data on infarct-related artery patency. Table 2 presents 90-minute, 180-minute, 24-hour, and 5–7 day patency values by TIMI flow grade for the three treatment regimens. Reocclusion rates were similar for all three treatment regimens.

Table 2

<table>
<thead>
<tr>
<th>Event</th>
<th>SK (IV) p-Value</th>
<th>SK (SQ) p-Value</th>
<th>SK (IV) p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-Minute</td>
<td>0.272</td>
<td>0.261</td>
<td>0.250</td>
</tr>
<tr>
<td>180-Minute</td>
<td>0.876</td>
<td>0.763</td>
<td>0.741</td>
</tr>
<tr>
<td>24-Hour</td>
<td>0.287</td>
<td>0.197</td>
<td>0.179</td>
</tr>
<tr>
<td>5–7 Day</td>
<td>0.475</td>
<td>0.775</td>
<td>0.713</td>
</tr>
</tbody>
</table>

The exact relationship between coronary artery patency and clinical activity has not been established. The safety and efficacy of the accelerated infusion of Alteplase have not been evaluated using antiplatelet or antiplatelet regimens other than those used in the GUSTO trial.

3-Hour Infarct in AMI Patients

In patients studied in a controlled trial with coronary angiography at 90 and 120 minutes following infusion of Alteplase, infarct artery patency was observed in 71% and 85% of global perfusion (n=65), respectively. In a second study, an angiographic angiography prior to and following infusion of Alteplase within 6 hours of the onset of symptoms showed that the obstructed vessel occurred within 90 minutes after the commencement of therapy in 71% of 83 patients. The exact relationship between coronary artery patency and clinical activity has not been established.

In a double-blind, randomized trial (138 patients) comparing Alteplase to placebo, patients infused with Alteplase within 4 hours of onset of symptoms experienced improved left ventricular function to Day 10 compared to the placebo group. Infarction fraction was measured by gated blood pool scan (53.2% vs 46.4%, p=0.018). Relative to baseline (Day 1) values, the net change of ejection fraction were +12% and +4% for the treated and placebo groups, respectively (p=0.0001). Also documented was a reduced incidence of clinical congestive heart failure in the treated group (14%) compared to the placebo group (35%) (p<0.0005). In a second trial, randomized (160 patients) comparing Alteplase to placebo, patients infused with Alteplase within 2.5 hours of onset of symptoms experienced improved left ventricular function at a mean of 21 days compared to the placebo group, when ejection fraction was measured by gated blood pool scan (52% vs 48%, p=0.08) and by contrast ventriculogram (61% vs 54%, p=0.006). Although the contribution of Alteplase alone is unclear, the incidence of minor neurological deficit was lower (13.1%, p=0.008). In a second study, where patients received coronary angiography before and after infusion of placebo, patients infused with Alteplase within 5 hours of the onset of symptoms of acute myocardial infarction experienced improved 30-day survival compared to placebo. At 1 month, the overall mortality rates were 7.2% for the Alteplase-treated group and 9.8% for the placebo-treated group (p=0.001). This benefit was maintained at 6 months for Alteplase-treated patients (10.4%) compared to those treated with placebo (13.1%, p=0.008).

In a double-blind, randomized trial (721 patients) comparing Alteplase to placebo, patients infused with Alteplase within 5 hours of the onset of symptoms experienced improved left ventricular function 10–22 days after treatment compared to the placebo group, when ventricular function was measured by echocardiography (33.7% vs 48.5%, p=0.031). Patients treated with Alteplase had a 19% reduction in infarct size, as measured by current release release of MB (c- MB) compared to placebo. Mortality at 1 month in the Alteplase-treated patients was reduced to 3.7% compared to 6.3% in placebo-treated patients (p<0.001). Patients treated with Alteplase had significantly fewer episodes of cardiacogenic shock (p=0.02), ventricular fibrillation (p<0.04) and pericarditis (p=0.01) compared to patients treated with placebo. Mortality at 1 month in the Alteplase-treated patients was reduced to 3.7% compared to 6.3% in placebo-treated patients (1-sided p=0.05). Although these data do not demonstrate unequivocally a significant reduction in mortality in this study, they do indicate a trend that is supported by the results of the ASSET study.

Acute Ischemic Stroke Patients

Two-placebo-controlled, double-blind trials (The NIHSS-1-Pa Stroke Trial, Part 1 and Part 2) have been conducted in patients with acute ischemic stroke. Both studies enrolled patients with a variable neurological deficit who were treated within 3 hours from symptom onset. In a randomized computerized tomography (CT) scan was performed prior to treatment to rule out the presence of intracranial hemorrhage (ICH). Patients were also included for the presence of conditions related to risks of bleeding (see CONTRAINDICATIONS), for minor neurological deficit, for rapidly improving symptoms prior to initiating study treatment, or for blood glucose of < 50 mg/dl or > 400 mg/dl. Patients were randomized to receive 0.9 mg/kg (maximum of 90 mg) or placebo. Alteplase was administered as a 10% initial bolus over 1 minute followed by continuous intravenous infusion of 10 mg/hour for 45 minutes (see DOSAGE AND ADMINISTRATION). In patients without recent use of oral anticoagulants or heparin, study treatment was initiated prior to the oral administration of anticoagulants. The initial study (NINDS Part-1, n=291) evaluated neurological improvement at 24 hours after onset of symptoms. The primary endpoint, the proportion of patients with a 4 or more point improvement in the National Institutes of Health Stroke Scale (NIHSS) score or complete recovery (NIHSS score = 0), was significantly different between treatment groups. A secondary analysis suggested improved 3-month outcome associated with Alteplase treatment using the following stroke assessment scales: Barthel index, Modified Rankin Scale, Glasgow Outcome Scale, and the NIHSS. A second study (NINDS-Part-2, n=333) assessed clinical outcome at 3 months as the primary outcome. A favorable outcome was defined as a minimum of 32 points on the Generalized Estimating Equations and individually are presented in Table 3. This study, depending upon the scale, the proportion of patients with minimal or no disability occurred in at least 11 per 100 more patients treated with Alteplase than those receiving placebo. Secondary analyses demonstrated consistent functional and neurological improvement within all four stroke scales as indicated by median scores. These results were highly consistent with the 3-month outcome treatment effects observed in the Part 1 study.
**ACTIVASE® (Alteplase)**

- Recent intracranial or intraspinal surgery or trauma (see WARNINGS)
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled hypertension

**Acute Ischemic Stroke**

Activase therapy in patients with acute ischemic stroke is contraindicated in the following situations because of an increased risk of bleeding, which could result in significant disability or death:

- Evidence of intracranial hemorrhage on pretreatment evaluation
- Suspicion of subarachnoid hemorrhage on pretreatment evaluation
- Recent (within 3 months) intracranial or infrasphenoid, serious head trauma, or previous stroke
- History of intracranial hemorrhage
- Uncontrolled hypertension at time of treatment (e.g., > 185 mm Hg systolic or > 110 mm Hg diastolic)
- Seizure at the onset of stroke
- Active intracranial bleeding
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis including but not limited to:
  - Current use of oral anticoagulants (e.g., warfarin sodium) or an International Normalized Ratio (INR) > 1.7 or a prothrombin time (PT) > 15 seconds
  - Administration of heparin within 48 hours preceding the onset of stroke and have an elevated activated partial thromboplastin time (aPTT) at presentation

**WARNINGS**

Bleeding

The most common complication encountered during Activase therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts
- Superficial or surface bleeding, observed mainly at invaded or distended sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention)

The concomitant use of heparin-anticoagulant therapy may also lead to bleeding. Some of the hemorrhage episodes occurred 1 or more days after the effects of Activase had dissipated, but while heparin therapy was continuing.

In the following conditions, the risks of Activase therapy for all approved indications may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Carotid endarterectomy
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP ≥ 175 mm Hg and/or diastolic BP ≥ 110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Nephromatosis defects including those secondary to severe hepatic or renal disease
- Significant hepatic dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic changes
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (e.g., over 75 years old)
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

**Cholesterol Embolization**

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

**Use in Acute Myocardial Infarction**

In a small subgroup of AMI patients who are at low risk for death from cardiac causes (i.e., no previous myocardial infarction, Killip class I) and who have high blood pressure at the time of presentation, the risk for stroke may offset the survival benefit produced by thrombolytic therapy.

**Arrhythmias**

Coronary thrombosis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of Activase are administered.

**Use in Acute Ischemic Stroke**

In addition to the previously listed conditions, the risks of Activase therapy to treat acute ischemic stroke may be increased in the following conditions and should be weighed against the anticipated benefits:

- Patients with severe neurological deficit (e.g., NIHSS > 22) at presentation. There is an increased risk of intracranial hemorrhage in these patients
- Patients with major early infarct signs on a computed cranial tomography (CT) scan (e.g., substantial edema, mass effect, or midline shift)
- Patients without recent use of oral anticoagulants or heparin, Activase treatment can be initiated prior to the availability of coagulation study results. However, infusion should be discontinued if either a pretreatment International Normalized Ratio (INR) > 1.7 or a prothrombin time (PT) > 15 seconds or an elevated activated partial thromboplastin time (aPTT) is identified.

Treatment should be limited to facilities that can provide appropriate evaluation and management of ICH.
ACTIVASE® (Alteplase)

In acute ischemic stroke, neither the incidence of intracranial hemorrhage nor the benefits of therapy are known for patients treated with Activase 3 hours after the onset of symptoms. Therefore, treatment of patients with acute ischemic stroke more than 3 hours after symptom onset is not recommended. Due to the increased risk for misdiagnosis of acute ischemic stroke, special diligence is required in making this diagnosis in patients whose blood glucose values are < 50 mg/dL or > 400 mg/dL. The safety and efficacy of treating patients with an evolving neurological deficit or with rapidly improving symptoms prior to the start of Activase administration have not been evaluated. Therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.

Use in Pulmonary Embolism

It should be recognized that the treatment of pulmonary embolism with Activase has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS

General

Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with Activase treatment. Noncompressible arterial puncture sites must be avoided and thorough bleeding control must be achieved and venous punctures should be minimized. In the event of serious bleeding, Activase and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Oroking angioedema has been observed in post-market experience in patients treated for acute ischemic stroke and in patients treated for acute myocardial infarction (see PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Allergic Reactions). Onset of angioedema occurred during and up to 2 hours after infusion of Activase. In many cases, patients were receiving concomitant Angiotensin-converting enzyme inhibitors. Patients treated with Activase should be monitored during and for several hours after infusion for signs of orolingual angioedema. If angioedema is noted, promptly institute appropriate therapy (oral or intravenous corticosteroids or epinephrine) and consider discontinuing the Activase infusion. Rare fatal cases of hemorrhage associated with traumatic intubation in patients administered Activase have been reported.

Readministration

There is no experience with readministration of Activase. If an anaphylactoid reaction occurs, the patient should be treated with conventional therapy. Although sustained antibody formation in patients receiving one dose of Activase has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (single point measurement) were reported in one patient, but subsequent antibody test results were negative.

Drug/Laboratory Test Interactions

During Activase therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent in vitro activations. Activase is an enzyme that when present in blood in pharmacologic concentrations remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of fibrinogen will result in inaccurate (150-200 units/ml) to some extent mitigate this phenomenon.

Drug Interactions

The interaction of Activase with other cardiovascular or cerebrovascular drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole and Ticlopidine) may increase the risk of bleeding when administered with, or after Activase therapy. There have been post-marketing reports of orolingual angioedema associated with the use of Activase. Many patients, primarily acute ischemic stroke patients, were receiving concomitant Angiotensin-converting enzyme inhibitors. (See PRECAUTIONS: General and ADVERSE REACTIONS: Allergic Reactions). Use of Antithrombotics

Aspirin and heparin have been administered concomitantly with and following infusions of Activase in the management of acute myocardial infarction or pulmonary embolism. Because the safety profile of aspirin or heparin alone has not been evaluated in the presence of the hemostatic plug formed at needle puncture sites, Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Activase therapy. Therefore, Activase therapy requires careful attention to potential bleeding sites, e.g., catheter insertion sites, and arterial puncture sites.

Allergic Reactions

Aspirin and heparin have been administered concomitantly with and following infusions of Activase in the management of acute myocardial infarction or pulmonary embolism. Because the safety profile of aspirin or heparin alone has not been evaluated in the presence of the hemostatic plug formed at needle puncture sites, Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Activase therapy. Therefore, Activase therapy requires careful attention to potential bleeding sites, e.g., catheter insertion sites, and arterial puncture sites.

Antiplatelet drugs and heparin should be monitored frequently and controlled during and following Activase administration in the management of acute ischemic stroke. In the TINDS-1 PA Stroke Trial, blood pressure was actively controlled (≤ 185/110 mm Hg) for 24 hours. Blood pressure was monitored during the hospital stay.

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, which evaluated tumorigenicity of Activase and effect on tumor metastasizein rodents, were negative. 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 and only at the highest concentrations tested.

Pregnancy (Category C)

Activase has been shown to have an embryocidal effect in rabbits when intravenously administered in doses of approximately twice (3 mg/kg) the human dose for AMI. No maternal or embryonic toxicity was observed at a time (1 mg/kg) the human dose, pregnant rats and rabbits were given during the period of organogenesis. There are no adequate and well-controlled studies in pregnant women. 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 Activase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if the Activase is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Activase in pediatric patients have not been established.

ADVERSE REACTIONS

Bleeding

The most frequent adverse reaction associated with Activase in all approved indications is bleeding (see WARNINGS).14,15

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial, or venous) occur, Activase therapy should be discontinued immediately, along with any concomitant therapy with heparin. Death and permanent disability are not uncommonly observed in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

In the GUSTO trial for the treatment of acute myocardial infarction, using the accelerated infusion regimen the incidence of all strokes for the Activase-treated patients was 1.6% while the incidence of nonfatal stroke was 0.3%. The incidence of hemorrhagic stroke was 0.7%, not all of which were fatal. The incidence of all strokes, as well as that for hemorrhagic stroke, increased with increasing age (see CLINICAL PHARMACOLOGY: Accelerated Infusion in AMI Patients). Data from previous trials utilizing a 3-hour infusion of ≤ 150 mg indicated that the incidence of total stroke in six randomized double-blind placebo-controlled trials14,15,2,7 was 1.2% (37/3161) in Alteplase-treated patients compared with 0.9% (27/3092) in placebo-treated patients. For the occurrence of significant internal bleeding (estimated as > 250 cc blood loss) has been reported in studies in over 800 patients. These data do not include patients treated with the Alteplase accelerated infusion.

Dose

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>ICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg, 3-hour</td>
<td>3272</td>
</tr>
<tr>
<td>≤ 100 mg, accelerated</td>
<td>10,396</td>
</tr>
<tr>
<td>150 mg</td>
<td>1779</td>
</tr>
<tr>
<td>1–1.4 mg/kg</td>
<td>237</td>
</tr>
</tbody>
</table>

These data indicate that a dose of 150 mg of Activase should not be used in the treatment of AMI because it has been associated with an increase in intracranial bleeding.14,15

For acute massive pulmonary embolism, bleeding events were consistent with the general safety profile observed with Activase in acute myocardial infarction patients receiving the 3-hour infusion regimen. The incidence of ICH, especially symptomatic ICH, in patients with acute ischemic stroke was higher in Activase-treated patients than placebo patients (see CLINICAL PHARMACOLOGY).

A study of another alteplase product, Actilyse, in acute ischemic stroke, suggested that doses greater than 0.9 mg/kg may be associated with an increased incidence of ICH.14 Doses greater than 0.9 mg/kg (maximum 90 mg) should not be used in the management of acute ischemic stroke.

Bleeding events other than ICH were noted in the studies of acute ischemic stroke and were consistent with the general safety profile of Activase. In The NINDS t-PA Stroke Trial (Parts 1 and 2), the frequency of bleeding requiring red blood cell transfusions was 6.4% for Activase-treated patients compared to 3.8% for placebo (p=0.19). Using Mantel-Haenszel Chi-Square analysis, there have been rare fatalities as a result of upper airway hemorrhage from intubation trauma.

Other Adverse Reactions

The following adverse reactions have been reported among patients receiving Activase in clinical trials and in post-marketing experience. These reactions are frequent sequelae of the underlying disease and the effect of Activase on the incidence of these events is unknown. Use in Acute Ischemic Infarction: Arhythmias, AV block, cardiogenic shock, heart failure, cardiac arrest, recurrent ischemia, myocardial reinfarction, myocardial rupture, electro-mechanical dissociation, pericardial effusion, pericarditis, mitral regurgitation, cardiac tamponade, thromboembolism, pulmonary edema. These events may be life threatening and may lead to death. Nausea and/or vomiting, hypotension and fever have also been reported.

Use in Pulmonary Embolism: Pulmonary reembolization, pulmonary edema, pleural effusion, thromboembolism, hypotension. These events may be life threatening and may lead to death. Fever has also been reported. Use in Acute Ischemic Stroke: Cerebral edema, cerebral hemorrhage, seizure, new ischemic stroke. These events may be life threatening and may lead to death.

DOSE AND ADMINISTRATION

Activase (Alteplase) for intravenous administration only. Extravasation of Activase infusion can cause ecchymosis and/or inflammation. Management consists of terminating the infusion at that IV site and application of local therapy.

Acute Myocardial Infarction

Administer Activase as soon as possible after the onset of symptoms.

There are two Activase dose regimens for use in the management of acute myocardial infarction: concomitant studies to compare clinical outcomes with these regimens have not been conducted.

A DOSE OF 150 MG OF ACTIVASE SHOULD NOT BE USED FOR THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Accelerated Infusion

The recommended total dose is based upon patient weight. Not to exceed 100 mg. For patients weighing > 67 kg, the recommended dose administered is 100 mg as a 15 mg intravenous bolus, followed by 50 mg infused over the next 30 minutes, and then 35 mg infused over the next 60 minutes. For patients weighing ≤ 67 kg, the recommended dose is administered as a 15 mg intravenous bolus, followed by 0.75 mg/kg infused over the next 30 minutes not to exceed 50 mg, and then 0.50 mg/kg over the next 60 minutes not to exceed 35 mg. The safety and efficacy of this accelerated infusion of Activase has been investigated in concomitant administration of heparin and aspirin as described in CLINICAL PHARMACOLOGY.
**ACTIVASE®** (Alteplase)

**How Supplied**

ACTIVASE® (Alteplase) is supplied as a sterile, lyophilized powder in 50 mg vials containing vacuum and in 100 mg vials without vacuum.

Each 50 mg Activase vial (29 million IU) is packaged with diluent for reconstitution (50 mL Sterile Water for Injection, USP); NDC 59242-044-13.

Each 100 mg Activase vial (58 million IU) is packaged with diluent for reconstitution (100 mL Sterile Water for Injection, USP), and one device vial: NDC 59242-085-27.

**Storage**

- Activase® is stabilized at room temperature not to exceed 30°C (86°F), or under refrigeration (2–8°C/36–46°F). Protect the lyophilized material during extended storage from excessive exposure to light.
- Do not use beyond the expiration date stamped on the vial.

**References**


2. Califf RM, Topol EJ, George BS, et al. Hemorrhagic complications associated with the


5. O'Rourke M, Baron D, Keogh A, et al. Limitation of myocardial infarction by early


12. Lancet.


15. Thromb Haemostas.


17. JAMA.


22. JAMA.
