For your acute ischemic stroke (AIS) patients
The first 24 hours are critical when t-PA therapy is administered\(^1\)\(^-\)\(^3\)

- 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 in patient recovery

Use the t-PA Checklist as a guide in tracking your patients’ needs\(^1\)\(^-\)\(^3\)

### During t-PA therapy

- **Perform neurologic assessments**
  - A full NIHSS assessment should be performed on the patient upon admission.
  - Repeat every 15 minutes during the 1-hour infusion to monitor for neurologic deterioration

- **Check for major and/or minor bleeding**
  - Assess urine, nares, gums, skin, stool, and emesis.
  - Major bleeding: intracranial, retroperitoneal, gastrointestinal, or genitourinary hemorrhages
  - Minor bleeding: gums, venipuncture sites, hematuria, hemoptysis, 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
  - Increase the frequency of blood pressure measurements if systolic blood pressure is \(\geq 180\) mm Hg or if diastolic blood pressure is \(\geq 105\) 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 changes in level of consciousness, deterioration of neurologic status, severe headache, pupillary changes, nausea/vomiting, or acute hypertension

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

### Post t-PA 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 was 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 was stopped

- **Obtain a follow-up CT scan or MRI** at 24 hours before starting anticoagulants or antiplatelet agents

- Adapted from the American Heart Association/American Stroke Association (AHA/ASA) and American Association of Neuroscience Nurses (AANN) Guidelines.

### Professional organizations support treatment with Activase Alteplase (t-PA)\(^1\)\(^-\)\(^3\)

- The AHA/ASA support Activase (t-PA) use in eligible AIS patients within 3 hours of symptom onset
- 2007 AHA/ASA Guidelines for the Early Management of Adults With Ischemic Stroke continues to give Activase (t-PA) a Class I, Level of Evidence A recommendation

**Note:** Each of these guidelines or policy statements represents only 1 possible approach to the treatment of eligible AIS 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.

Class I conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

Level of Evidence A data derived from multiple randomized clinical trials.

**References:**
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>
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</thead>
</table>

Chart time: Neurologic assessment:

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>
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</table>

Chart time: Neurologic assessment:

Hourly until 24 hours after infusion

<table>
<thead>
<tr>
<th>Hours:</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<th>15</th>
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<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
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</table>

Chart time: Neurologic assessment:

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>
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Chart time: BP:

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Chart time: BP:

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<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
</tr>
</thead>
</table>

Chart time: BP:

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).

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.
DESCRIPTION

Activase® (Alteplase) is a tissue plasminogen activator 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-type plasminogen activator obtained from a human cell line. The manufacturing process involves the secretion of the enzyme activase 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 nutrient medium containing the antibiotic gentamicin, 100 mg/L. However, the presence of the antibiotic is not detectable in the final product. Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Activase is a sterile, white to off-white, lyophilized powder for intravenous administration after reconstitution with Sterile Water for Injection, USP.

Quantitative Composition of the Lyophilized Product

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
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</thead>
<tbody>
<tr>
<td>Activase</td>
<td>100 mg Vial</td>
</tr>
<tr>
<td></td>
<td>50 mg Vial</td>
</tr>
<tr>
<td>L-Arginine</td>
<td>3.5 g</td>
</tr>
<tr>
<td>Phosphoric Acid</td>
<td>1 g</td>
</tr>
<tr>
<td>Polyborate 80</td>
<td>≤ 11 mg</td>
</tr>
<tr>
<td>Vacuum</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Biological potency is determined by an in vitro clot lysis assay and is expressed in International Units as treated against the WHO standard. The specific activity of Activase is 580,000 IU/mg.

CLINICAL PHARMACOLOGY

Activase is an enzyme (serine protease) which has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When introduced into the systemic circulation at pharmacologic concentrations, Activase rapidly converts the plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Following administration of 100 mg Activase, there is a decrease (16%–38%) in circulating fibrinogen. Activase is a continuous activator of the plasminogen-plasmin system (90 mg/kg body weight over 3 hours) experienced a decrease in fibrinogen to below 100 mg/dL.1

The clearance of Activase in AMI patients has shown that it is rapidly cleared from the plasma with a mean half-life of 6 minutes. There is no difference in the dominant initial plasma half-life between the 3-Hour and accelerated regimens for AMI. The plasma clearance of Activase is 380–570 mL/min.1 The clearance is mediated primarily by the liver, with the initial volume of distribution approximately plasma volume.

Acute Myocardial Infarction (AMI) Patients

Coronary occlusion due to a thrombus is present in the infarct related coronary artery in approximately 80% of patients experiencing a transmural myocardial infarction evaluated within 4 hours of onset of symptoms.2,3 Two Activase dose regimens have been studied in patients experiencing acute myocardial infarction. Entry criteria included onset of chest pain within 6 hours of treatment and ST-segment elevation of ECG. The regimens included accelerated infusion of Activase (< 100 mg over 90 minutes, see DOSAGE AND ADMINISTRATION) plus intravenous (IV) heparin (accelerated 3-Hour Infusion in AMI Patients) or placebo (see CONTRAINDICATIONS), for minor neurological deficit, for rapidly improving symptoms (ICH). Patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computed tomography (CT) scan was obtained prior to treatment to rule out the presence of intracranial hemorrhage (ICH). Patients were also excluded for the presence of conditions related to risks of bleeding (see CONTRAINDICATIONS), for minor neurological deficit, for rapidly improving symptoms (ICH). Patients were randomized to receive placebo or Activase within 6 hours of the onset of symptoms, reperfusion was established in 71% of 83 patients.1

3-Hour Infusion in AMI Patients

| Table 1
<table>
<thead>
<tr>
<th>Event</th>
<th>Accelerated Activase SK (IV)</th>
<th>p-Value*</th>
<th>SK (SQ)</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day Mortality</td>
<td>6.3%</td>
<td>7.3%</td>
<td>0.003</td>
<td>7.3%</td>
</tr>
<tr>
<td>30-Day Morbidity or Nonfatal Stroke</td>
<td>7.2%</td>
<td>8.0%</td>
<td>0.065</td>
<td>8.0%</td>
</tr>
<tr>
<td>24-Hour Mortality</td>
<td>2.4%</td>
<td>2.9%</td>
<td>0.009</td>
<td>2.8%</td>
</tr>
<tr>
<td>Intracerebral Hemorrhage</td>
<td>1.6%</td>
<td>1.4%</td>
<td>0.32</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

*Two-tailed p-value is for comparison of Accelerated Activase to the respective SK control arm.

Subgroup analysis of patients by age, infant location, time from symptom onset to thrombolysis, and treatment in the U.S. or elsewhere showed consistently lower 30-day mortality for the Activase accelerated infusion group. For patients who were over 75 years of age, a predefined subgroup consisting of 12% of patients enrolled, the incidence of stroke was 3.0% for the placebo accelerated infusion group, 2.8% for SK (IV), and 3.2% for SK (SQ); the incidence of combined 30-day mortality or nonfatal stroke was 29.6%.

ACIVETASE® (Alteplase)

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 shows patency at 90–minute, 180-minute, and 24-hour time points. 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>Accelerated Activase SK (IV)</th>
<th>p-Value</th>
<th>SK (IV)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90–Minute</td>
<td>272</td>
<td>281</td>
<td>0.32</td>
<td>260</td>
</tr>
<tr>
<td>180–Minute</td>
<td>80</td>
<td>76</td>
<td>0.001</td>
<td>95</td>
</tr>
<tr>
<td>24-Hour</td>
<td>61</td>
<td>72</td>
<td>0.029</td>
<td>67</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 antithrombotic or antiplatelet regimens other than those used in the GUSTO trial.

Two Accelerated Activase dose regimens were studied in patients treated in a controlled trial with coronary angiography at 90 and 120 minutes following infusion of Activase, intact artery patency was observed in 71% and 85% of patients, respectively.4,5 Relative to baseline (Day 1) values, the net changes in ejection fraction were +3.6% and +4.7% for the treated and placebo groups, respectively (p < 0.001). Also documented was a reduced incidence of clinical coronary heart disease in the treated group (14%) compared to the placebo group (33%) (p < 0.008).

In a double-blind, randomized trial (145 patients) comparing Activase to placebo, patients infused with Activase had a 2.5 hours of onset of symptoms experienced improved ventricular function at a mean of 21 days compared to the placebo group, whose ventricular function was measured by gated blood pool scan (52% vs 48%, p = 0.08) and by contrast ventriculogram (61% vs 54%, p = 0.008). Although the contribution of Activase alone is unclear, the incidence of nonischemic heart failure was lower in the treated group at a rate of 6.7% (e.g., congestive heart failure, pericarditis, atrial fibrillation, and conduction disturbance) was reduced when compared to those patients treated with placebo (p < 0.01).

In a double-blind, randomized trial (721 patients) comparing Activase to placebo, patients infused within 5 hours of the onset of symptoms experienced improved ventricular function at 10–22 days treatment compared to the placebo group, when global ejection fraction was measured by contrast ventriculography (50.7% vs 48.5%, p = 0.01). Patients treated with Activase had a 19% reduction in infarct size, as measured by cumulative release of creatine kinase (CK) activity (12% vs 11%) when compared to placebo treated patients (p = 0.001).6 Patients treated with Activase had significantly fewer episodes of cardiogenic shock (p = 0.02), ventricular fibrillation (p < 0.04) and pericarditis (p = 0.01) compared to patients treated with placebo. Mortality at 21 days in Activated treated patients was reduced to 3.7% compared to 6.3% in placebo treated patients (p < 0.05). Although these data do not demonstrate unequivocally a significant reduction in mortality for Activase, they do indicate a trend that is supported by the results of the ASSENT study.

Acute Ischemic Stroke Patients

Two placebo-controlled, double-blind trials (The NINDS IS-1 Stroke Trial, Part 1 and Part 2) have been conducted in patients treated with placebo and stroke patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computed tomography (CT) scan was obtained prior to treatment to rule out the presence of intracranial hemorrhage (ICH). Patients were also excluded for the presence of conditions related to risks of bleeding (see CONTRAINDICATIONS), for minor neurological deficit, for rapidly improving symptoms (ICH). Patients were randomized to receive either 0.9 mg/kg Activase (maximum of 90 mg), or placebo. Activase was administered as a 10% initial bolus followed by continuous intravenous infusion of the remainder over 60 minutes (see DOSAGE AND ADMINISTRATION).

In patients without recent use of oral anticoagulants or heparin, treatment started study regimen for an initial period of 3–5 days. Patients treated with Activase had 4.0% of patients treated with placebo (p = 0.01). Though these data do not demonstrate unequivocally a significant reduction in mortality for Activase, they do indicate a trend that is supported by the results of the ASSENT study.
**ACTIVASE**<sup>®</sup> (Alteplase)

### Table 3
The NINDS I-P A Stroke Trial, Part 2
3-Month Efficacy Outcomes

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo (n=165)</th>
<th>Activase (n=168)</th>
<th>Absolute Difference (95% CI)</th>
<th>p-Value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Estimating Equations (Multivariate)</td>
<td>—</td>
<td>—</td>
<td>1.34 (1.05, 1.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>37.6%</td>
<td>50.0%</td>
<td>12.4% (3.0, 21.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Modified Rankin Scale</td>
<td>26.1%</td>
<td>38.7%</td>
<td>12.6% (3.7, 21.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Glasgow Outcome Scale</td>
<td>31.5%</td>
<td>44.0%</td>
<td>12.5% (3.3, 21.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>NIHSS</td>
<td>20.0%</td>
<td>31.0%</td>
<td>11.0% (2.6, 19.3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<sup>1</sup>Favorable Outcome is defined as recovery with minimal or no disability.

<sup>2</sup>Value < 1 indicates frequency of recovery in favor of Activase treatment.

<sup>3</sup>p-Value for Relative Frequency is from Generalized Estimating Equations with Log link.

The incidences of all-cause 90-day mortality, ICH, and new ischemic stroke following Activase treatment compared to placebo are presented in Table 4 as a combined safety analysis (n=624) for Parts 1 and 2. The overall incidence of all-cause death following Activase treatment, particularly symptomatic ICH within 36 hours. In Activase-treated patients, there were no increases compared to placebo in the incidences of 90-day mortality or severe disability.

### Table 4
The NINDS I-P A Stroke Trial
Safety Outcomes: Part 1 and Part 2 Combined

<table>
<thead>
<tr>
<th>Placebo (n=312)</th>
<th>Activase (n=315)</th>
<th>p-Value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause 90-day Mortality</td>
<td>64 (20.5%)</td>
<td>54 (17.3%)</td>
</tr>
<tr>
<td>Total ICH&lt;sup&gt;1&lt;/sup&gt;</td>
<td>20 (6.4%)</td>
<td>48 (15.4%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>4 (1.3%)</td>
<td>25 (8.0%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>16 (5.1%)</td>
<td>23 (7.4%)</td>
</tr>
<tr>
<td>Symptomatic ICH within 36 hours</td>
<td>2 (0.6%)</td>
<td>20 (6.4%)</td>
</tr>
<tr>
<td>New Ischemic Stroke (3-months)</td>
<td>17 (5.4%)</td>
<td>18 (5.8%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Within trial follow-up period. Symptomatic ICH was defined as the occurrence of sudden clinical worsening followed by subsequent verification of ICH on CT scan. Asymptomatic ICH was defined as ICH detected on a routine repeat CT scan without preceding clinical worsening.

<sup>2</sup>Fisher’s Exact Test

In a prespecified subgroup analysis in patients receiving aspirin prior to onset of stroke symptoms, there was preserved favorable outcome compared with placebo in activase-treated patients. In exploratory, multivariate analyses of both studies combined (n=624) to investigate potential predictors of ICH and treatment effect modifiers were performed. In Activase-treated patients presenting with severe neurological deficit at presentation (e.g., NIHSS > 22) or of advanced age (e.g., > 77 years of age), the trends toward increased risk for symptomatic ICH within the first 36 hours were more prominent. Similar trends were also seen for total ICH and for all-cause 90-day mortality in these patients. When risk was adjusted for the combination of death and severe disability in these patients, there was no difference between placebo and Activase groups.

Analyses for efficacy suggested a reduced but still favorable clinical outcome for Activase-treated patients with severe neurological deficit or advanced age at presentation.

### Pulmonary Embolism

**Part 1** and **Part 2** Combined

In a comparative randomized trial (n=45),<sup>14</sup> 59% of patients (n=22) treated with Activase (100 mg over 2 hours) experienced moderate or marked lysis of pulmonary emboli when assessed by pulmonary angiography 2 hours after treatment initiation. Activase-treated patients also experienced a significant reduction in pulmonary embolism-induced pulmonary hypertension (p=0.003). Pulmonary perfusion at 24 hours, as assessed by radionuclide scan, was significantly improved (p<0.002) in Activase-treated patients compared with placebo.

### INDICATIONS AND USAGE

#### Acute Myocardial Infarction

**Activase**<sup>®</sup> (Alteplase) is indicated for use in the management of acute myocardial infarction in adults for the improvement of ventricular function following AMI, the reduction of incidence of congestive heart failure, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

#### Acute Ischemic Stroke

**Activase**<sup>®</sup> (Alteplase) is indicated for the management of acute ischemic stroke in patients with signs and symptoms associated with thrombotic, embolic, or other vascular occlusion. Treatment should be initiated by an experienced physician capable of initiating appropriate therapy for the acute ischemic stroke.

#### Acute Ischemic Stroke

**Activase**<sup>®</sup> (Alteplase) is indicated for the management of acute ischemic stroke in patients with signs and symptoms associated with thrombotic, embolic, or other vascular occlusion. Treatment should be initiated by an experienced physician capable of initiating appropriate therapy for the acute ischemic stroke.

**CONTRAINDICATIONS**

#### Acute Myocardial Infarction or Pulmonary Embolism

**Activase**<sup>®</sup> (Alteplase) is indicated in the management of acute massive pulmonary embolism (PE) in adults:
- For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lung.
- For the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

**ACTIVASE**<sup>®</sup> (Alteplase)

- 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:
- **Active internal bleeding**
- **History of cerebrovascular accident**
- **Recent intracranial or intraspinal surgery or trauma** (see WARNINGS)

**Cholesterol Embolization**

Cholesterol embolization has been reported rarely in patients treated with all types of thrombolytic agents. The 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 embolization may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrene 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.**14**

**Arrhythmias**

Coronary thrombosis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular fibrillation) are not different from those seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic therapies. It is recommended that antiarrhythmic therapy for bradyarrhythmia and tachyarrhythmia be initiated when inflations 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:
- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- **Cerebrovascular disease**
- 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 pancreatitis
- Acute bacterial endocarditis
- Hemodynamic defects including those secondary to severe hepatic or renal disease
- Significant hepatic dysfunction
- Septicemia
- Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (e.g., over 75 years of age)
- 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.**
**ACTIVASE® (Alteplase)**

In acute ischemic stroke, neither the incidence of intracranial hemorrhage nor the benefits of therapy are known in patients treated with Activase more than 3 hours after the onset of symptoms. Therefore, the 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 to ensure that the diagnosis in patients with blood glucose values are <30 mg/dl or >400 mg/dl. The safety and efficacy of treatment with Activase in patients with minimal neurological deficit or with rapidly improving symptoms prior to the start of Activase administration have not been established. Therefore, the treatment of patients with minimal 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 rebleeding due to the lysis of underlying deep venous thrombus should be considered.

**PRECAUTIONS**

**General**

Standard management of myocardial infarction or pulmonary embolism should be implemented concurrently with the use of Activase. Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from noncompressible sites. Arterial and venous punctures should be minimized. In the event of serious adverse events, the infusion of Activase should be discontinued immediately.

**Heparin effects can be reversed by protamine.**

**Drug/Laboratory Test Interactions**

During Activase therapy, coagulation tests and/or measures of fibrinolytic activity are performed; the results may be unreliable unless specific precautions are taken to prevent in vitro artifacts. 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 aprotinin (150–200 units/mL) can 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 aspirin, dipyridamole and Abciximab) may increase the risk of bleeding if administered prior to, during, or after Activase therapy. There have been post-marketing reports of oroolingual angioedema associated with the use of Activase, particularly acute ischemic stroke and in patients with acute coronary syndromes, receiving concomitant Angiotensin-converting enzyme inhibitors.

**Use of Antihypertensives**

Aspirin and heparin have been administered concomitantly with and following infusions of Activase in the management of acute myocardial infarction or pulmonary embolism. Because hypertension, aspirin, or heparin may cause or worsen bleeding, careful monitoring for bleeding is advised, especially at arterial puncture sites.

The concomitant use of heparin or aspirin during the first 24 hours following symptom onset was prohibited in the INtensive Dose t-PA Stroke Trial (T1 and 2). The frequency of bleeding requiring red blood cell transfusions was higher in Activase-treated patients compared to 3.8% for placebo (p=0.19, using Mantel-Haenszel Chi-Square).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on reproduction. Short-term studies, which evaluated tumorigenicity of Activase and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in rodents, were negative. 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**

Allergic-type reactions, e.g., anaphylactoid reaction, laryngeal edema, orolingual angioedema, rash, and urticaria have been reported. A cause and effect relationship to Activase therapy has not been established. When such reactions occur, they usually respond to conventional therapy. There have been post-marketing reports of orolingual angioedema associated with the use of Activase. Most reports were of patients treated for acute ischemic stroke; some reports were during evaluation for acute myocardial infarction. (See PRECAUTIONS: General and ADVERSE REACTIONS: Allergic Reactions). Use of Activase in patients with acute ischemic stroke was higher in Activase-treated patients than placebo patients (see CLINICAL PHARMACOLOGY).

**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 attributed to the sequence of the underlying disease and the effect of Activase on the incidence of these events is unknown.

**Use in Acute Myocardial Infarction:** Arrhythmia, AV block, cardiogenic shock, heart failure with acute renal failure (Bright's disease and heart failure), cardiogenic shock, 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 reperfusion, 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 herniation, seizure, new ischemic stroke, intracranial hematoma, may be life threatening.

**DOSEAGE AND ADMINISTRATION**

**ACTIVASE® (Alteplase)** For intravenous administration only. Extravasation of Activase infusion may result in local skin necrosis and intramuscular, intradermal or subcutaneous emphysema. Activase is for intravenous administration only. Extravasation of Activase infusion may result in local skin necrosis and intramuscular, intradermal or subcutaneous emphysema.

**Bleeding**

The most frequent adverse reaction associated with Activase in all approved indications is bleeding (see WARNINGS). Should bleeding occur at a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, Activase therapy should be discontinued immediately, along with any concomitant therapy with heparin. Death and permanent disability are not uncommonly reported in patients who develop Activase extravasates (intracutaneous or intramuscular) and safely, 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
ACTIVASE® (Alteplase)

100 mg Vial

Reconstitution should be carried out using the transfer device provided, adding the contents of the 100 mg vial of Activase for Injection, USP (SWFI) to the contents of the 100 mg vial of Activase powder. Light foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. Please refer to the accompanying Instructions for Reconstitution and Administration. 100 mg VIALS DO NOT CONTAIN VACUUM.

100 mg VIAL RECONSTITUTION

Sterile technique throughout.

1. Remove the protective flip-caps from one vial of Activase and one vial of Sterile Water for Injection, USP (SWFI).
2. Do not use beyond the expiration date stamped on the vial.

DO NOT USE IF VACUUM IS NOT PRESENT.

Reconstitution should be carried out using a large bore needle (e.g., 18 gauge) and a syringe, directly into the sterile Sterile Water for Injection, USP, into the lyophilized cake. DO NOT USE IF VACUUM IS NOT PRESENT. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. Please refer to the accompanying Instructions for Reconstitution and Administration. 100 mg VIALS DO NOT CONTAIN VACUUM.

No other medication should be added to infusion solutions containing Activase. Any unused infusion solution should be discarded.

HOW SUPPLIED

ACTIVASE® (Alteplase), is supplied as a sterile, lyophilized powder in 50 mg vials containing 25 mg of Alteplase in 50 mg vials and in 100 mg vials containing 50 mg of Alteplase in 100 mg vials.

Each 50 mg Activase vial (29 million IU) is packaged with diluent for reconstitution (50 mL Sterile Water for Injection, USP). NDC 50242-044-13.

Each 100 mg Activase vial (29 million IU) is packaged with diluent for reconstitution (100 mL Sterile Water for Injection, USP), and one transfer device. NDC 50242-085-27.

Storage

Store lyophilized Activase at controlled 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


ACTIVASE® (Alteplase)

7056206

Manufactured by:

GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080-4990

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