



## 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 tissue-type plasminogen activator obtained from a human melanoma cell line. The manufacturing process involves the 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, 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		
	100 mg Vial	50 mg Vial
Alteplase	100 mg (58 million IU)	50 mg (29 million IU)
L-Arginine	3.5 g	1.7 g
Phosphoric Acid	1 g	0.5 g
Polysorbate 80	≤ 11 mg	≤ 4 mg
Vacuum	No	Yes

Biological potency is determined by an in vitro clot lysis assay and is expressed in International Units as tested 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 concentration, Activase binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Following administration of 100 mg Activase, there is a decrease (16%–36%) in circulating fibrinogen.<sup>1,2</sup> In a controlled trial, 8 of 73 patients (11%) receiving Activase (1.25 mg/kg body weight over 3 hours) experienced a decrease in fibrinogen to below 100 mg/dL.<sup>2</sup>

The clearance of Alteplase in AMI patients has shown that it is rapidly cleared from the plasma with an initial half-life of less than 5 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 Alteplase is 380–570 mL/min.<sup>3,4</sup> The clearance is mediated primarily by the liver. The initial volume of distribution approximates 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.<sup>5,6</sup>

Two Activase dose regimens have been studied in patients experiencing acute myocardial infarction. (Please see DOSAGE AND ADMINISTRATION.) The comparative efficacy of these two regimens has not been evaluated.

## Accelerated Infusion in AMI Patients

Accelerated infusion of Activase was studied in an international, multi center trial (GUSTO) that randomized 41,021 patients with acute myocardial infarction to four thrombolytic regimens. 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 infusion of Alteplase, n=10,396), or the Kabikinase brand of Streptokinase (1.5 million units over 60 minutes) plus IV heparin (SK [IV], n=10,410), or Streptokinase (as above) plus subcutaneous (SQ) heparin (SK [SQ], n=9841). A fourth regimen combined Alteplase and Streptokinase. Aspirin and heparin use was directed by the GUSTO study protocol as follows: All patients were to receive 160 mg chewable aspirin administered as soon as possible, followed by 160–325 mg daily. IV heparin was directed to be a 5000 U IV bolus initiated as soon as possible, followed by a 1000 U/hour continuous IV infusion for at least 48 hours; subsequent heparin therapy was at the discretion of the attending physician. SQ heparin was directed to be 12,500 U administered 4 hours after initiation of SK therapy, followed by 12,500 U twice daily for 7 days or until discharge, whichever came first. Many of the patients randomized to receive SQ heparin received some IV heparin, usually in response to recurrent chest pain and/or the need for a medical procedure. Some received IV heparin on arrival to the emergency room prior to enrollment and randomization.

Results for the primary endpoint of the study, 30-day mortality, are shown in Table 1. The incidence of 30-day mortality for accelerated infusion of Alteplase was 1.0% lower than for SK (IV) and 1.0% lower than for SK (SQ). The secondary endpoints of combined 30-day mortality or nonfatal stroke, and 24-hour mortality, as well as the safety endpoints of total stroke and intracerebral hemorrhage are also shown in Table 1. The incidence of combined 30-day mortality or nonfatal stroke for the Alteplase accelerated infusion was 1.0% lower than for SK (IV) and 0.8% lower than for SK (SQ).

**Table 1**

Event	Accelerated Activase	SK (IV)	p-Value <sup>1</sup>	SK (SQ)	p-Value <sup>1</sup>
30-Day Mortality	6.3%	7.3%	0.003	7.3%	0.007
30-Day Mortality or Nonfatal Stroke	7.2%	8.2%	0.006	8.0%	0.036
24-Hour Mortality	2.4%	2.9%	0.009	2.8%	0.029
Any Stroke	1.6%	1.4%	0.32	1.2%	0.03
Intracerebral Hemorrhage	0.7%	0.6%	0.22	0.5%	0.02

<sup>1</sup>Two-tailed p-value is for comparison of Accelerated Activase to the respective SK control arm.

Subgroup analysis of patients by age, infarct location, time from symptom onset to thrombolytic treatment, and treatment in the U.S. or elsewhere showed consistently lower 30-day mortality for the Alteplase 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 4.0% for the Alteplase 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 20.6%

## ACTIVASE® (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 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**

Patency (TIMI 2 or 3)	Accelerated Activase	SK (IV)	p-Value	SK (SQ)	p-Value
90-Minute	n=272 81.3%	n=261 59.0%	< 0.0001	n=260 53.5%	< 0.0001
180-Minute	n=80 76.3%	n=76 72.4%	0.58	n=95 71.6%	0.48
24-Hour	n=81 88.9%	n=72 87.5%	0.24	n=67 82.1%	0.79
5–7 Day	n=72 83.3%	n=77 90.9%	0.47	n=75 78.7%	0.17

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.

## 3-Hour Infusion in AMI Patients

In patients studied in a controlled trial with coronary angiography at 90 and 120 minutes following infusion of Activase, infarct artery patency was observed in 71% and 85% of patients (n=85), respectively.<sup>2</sup> In a second study, where patients received coronary angiography prior to and following infusion of Activase within 6 hours of the onset of symptoms, reperfusion of the obstructed vessel occurred within 90 minutes after the commencement of therapy in 71% of 83 patients.<sup>1</sup>

The exact relationship between coronary artery patency and clinical activity has not been established.

In a double-blind, randomized trial (138 patients) comparing Activase to placebo, patients infused with Activase within 4 hours of onset of symptoms experienced improved left ventricular function at Day 10 compared to the placebo group, when ejection fraction was measured by gated blood pool scan (53.2% vs 46.4%, p=0.018). 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=0.0001). Also documented was a reduced incidence of clinical congestive heart failure in the treated group (14%) compared to the placebo group (33%) (p=0.009).<sup>7</sup>

In a double blind, randomized trial (145 patients) comparing Activase to placebo, patients infused with Activase 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 Activase alone is unclear, the incidence of nonischemic cardiac complications when taken as a group (i.e., congestive heart failure, pericarditis, atrial fibrillation, and conduction disturbance) was reduced when compared to those patients treated with placebo (p < 0.01).<sup>8</sup>

In a double-blind, randomized trial (5013 patients) comparing Activase to placebo (ASSET study), patients infused with Activase within 5 hours of the onset of symptoms of acute myocardial infarction experienced improved 30-day survival compared to those treated with placebo. At 1 month, the overall mortality rates were 7.2% for the Activase treated group and 9.8% for the placebo treated group (p=0.001).<sup>9,10</sup> This benefit was maintained at 6 months for Activase-treated patients (10.4%) compared to those treated with placebo (13.1%, p=0.008).<sup>10</sup>

In a double-blind, randomized trial (721 patients) comparing Activase to placebo, patients infused with Activase within 5 hours of the onset of symptoms experienced improved ventricular function 10–22 days after 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 HBD (α-hydroxybutyrate dehydrogenase) activity compared to placebo treated patients (p=0.001). 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 Activase treated patients was reduced to 3.7% compared to 6.3% in placebo treated patients (1-sided p=0.05).<sup>11</sup> Although these data do not demonstrate unequivocally a significant reduction in mortality for 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 NINDS t-PA Stroke Trial, Part 1 and Part 2) have been conducted in patients with acute ischemic stroke.<sup>12</sup> Both studies enrolled patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computerized tomography (CT) scan was performed 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 prior to initiating study treatment, or for blood glucose of < 50 mg/dL or > 400 mg/dL.

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 over 1 minute 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, study treatment was initiated prior to the availability of coagulation study results. However, the infusion was discontinued if either a pretreatment prothrombin time (PT) > 15 seconds or an elevated activated partial thromboplastin time (aPTT) was identified. Although patients with or without prior aspirin use were enrolled, administration of anticoagulants and antiplatelet agents was prohibited for the first 24 hours following symptom onset.

The initial study (NINDS-Part 1, n=291) evaluated neurological improvement at 24 hours after stroke onset. 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 not significantly different between treatment groups. A secondary analysis suggested improved 3-month outcome associated with Activase 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 minimal or no disability using the four stroke assessment scales: Barthel Index (score ≥ 95), Modified Rankin Scale (score ≤ 1), Glasgow Outcome Scale (score = 1), and NIHSS (score ≤ 1). The results comparing Activase- and placebo-treated patients for the four outcome scales together (Generalized Estimating Equations) and individually are presented in Table 3. In this study, depending upon the scale, the favorable outcome of minimal or no disability occurred in at least 11 per 100 more patients treated with Activase 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)

**Table 3** The NINDS t-PA Stroke Trial, Part 2  
3-Month Efficacy Outcomes

Analysis	Frequency of Favorable Outcome <sup>1</sup>				p-Value <sup>3</sup>
	Placebo (n=165)	Activase (n=168)	Absolute Difference (95% CI)	Relative Frequency <sup>2</sup> (95% CI)	
Generalized Estimating Equations (Multivariate)	—	—	—	1.34 (1.05, 1.72)	0.02
Barthel Index	37.6%	50.0%	12.4% (3.0, 21.9)	1.33 (1.04, 1.71)	0.02
Modified Rankin Scale	26.1%	38.7%	12.6% (3.7, 21.6)	1.48 (1.08, 2.04)	0.02
Glasgow Outcome Scale	31.5%	44.0%	12.5% (3.3, 21.8)	1.40 (1.05, 1.85)	0.02
NIHSS	20.0%	31.0%	11.0% (2.6, 19.3)	1.55 (1.06, 2.26)	0.02

<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. These data indicated a significant increase in ICH 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 t-PA Stroke Trial  
Safety Outcome

	Part 1 and Part 2 Combined		
	Placebo (n=312)	Activase (n=312)	p-Value <sup>2</sup>
All-Cause 90-day Mortality	64 (20.5%)	54 (17.3%)	0.36
Total ICH <sup>1</sup>	20 (6.4%)	48 (15.4%)	< 0.01
Symptomatic	4 (1.3%)	25 (8.0%)	< 0.01
Asymptomatic	16 (5.1%)	23 (7.4%)	0.32
Symptomatic ICH within 36 hours	2 (0.6%)	20 (6.4%)	< 0.01
New Ischemic Stroke (3-months)	17 (5.4%)	18 (5.8%)	1.00

<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 for Activase-treated patients. 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 (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 assessed by 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 Patients

In a comparative randomized trial (n=45),<sup>13</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 within 2 hours of treatment (p=0.003). Pulmonary perfusion at 24 hours, as assessed by radionuclide scan, was significantly improved (p=0.002).

### INDICATIONS AND USAGE

#### Acute Myocardial Infarction

Activase® (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 the 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® (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).**

#### Pulmonary Embolism

Activase® (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 lungs.
- 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.

### CONTRAINDICATIONS

#### Acute Myocardial Infarction or Pulmonary Embolism

Activase therapy in patients with acute myocardial infarction or pulmonary embolism 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)

## ACTIVASE® (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, 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 intraspinal surgery, 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 internal 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
  - Platelet count < 100,000/mm<sup>3</sup>

### 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 disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute 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.

As fibrin is lysed during Activase therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with Activase. Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary during an infusion of Activase, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of Activase and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with Activase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

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
- 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 pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Significant hepatic dysfunction
- Pregnancy
- 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 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.<sup>14</sup>

#### Arrhythmias

Coronary thrombolysis 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 computerized cranial tomography (CT) scan (e.g., substantial edema, mass effect, or midline shift).

In 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 in patients treated with Activase more than 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 treatment with Activase in patients with minor neurological deficit or with rapidly improving symptoms prior to the start of Activase administration has 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 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 bleeding, Activase and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Orolingual 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 (e.g. antihistamines, 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 infusion should be discontinued immediately and appropriate therapy initiated.

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 (a 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 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 cardioactive or cerebroactive 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 Abciximab) may increase the risk of bleeding if administered prior to, during, 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 heparin, aspirin, or Activase may cause bleeding complications, 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 were prohibited in The NINDS t-PA Stroke Trial. The safety of such concomitant use with Activase for the management of acute ischemic stroke is unknown.

#### Blood Pressure Control

Blood pressure should be monitored frequently and controlled during and following Activase administration in the management of acute ischemic stroke. In The NINDS t-PA Stroke Trial, blood pressure was actively controlled ( $\leq 185/110$  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 metastases in 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 two times (3 mg/kg) the human dose for AMI. No maternal or fetal toxicity was evident at 0.65 times (1 mg/kg) the human dose in pregnant rats and rabbits dosed 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 when 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).<sup>15,16</sup>

Should serious bleeding in 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 that 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

## ACTIVASE® (Alteplase)

the incidence of nonfatal stroke was 0.9%. 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  $\leq 100$  mg indicated that the incidence of total stroke in six randomized double blind placebo-controlled trials<sup>2,7-11,17</sup> was 1.2% (37/3161) in Alteplase treated patients compared with 0.9% (27/3092) in placebo-treated patients.

For the 3-hour infusion regimen, the incidence 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.

	Total Dose $\leq 100$ mg
gastrointestinal	5%
genitourinary	4%
ecchymosis	1%
retroperitoneal	< 1%
epistaxis	< 1%
gingival	< 1%

The incidence of intracranial hemorrhage (ICH) in acute myocardial infarction patients treated with Activase is as follows:

Dose	Number of Patients	ICH (%)
100 mg, 3-hour	3272	0.4
$\leq 100$ mg, accelerated	10,396	0.7
150 mg	1779	1.3
1–1.4 mg/kg	237	0.4

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.<sup>18</sup> 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.<sup>19</sup> **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).

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 of patients treated for acute myocardial infarctions (see PRECAUTIONS: General). Many of these patients received concomitant angiotensin-converting enzyme inhibitors (see PRECAUTIONS: Drug Interactions). Most cases resolved with prompt treatment; 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 Myocardial Infarction: Arrhythmias, AV block, cardiogenic shock, heart failure, cardiac arrest, recurrent ischemia, myocardial reinfarction, myocardial rupture, electromechanical 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 herniation, seizure, new ischemic stroke. These events may be life threatening and may lead to death.

#### DOSE AND ADMINISTRATION

Activase® (Alteplase) is 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; controlled 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  $\leq 67$  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 Alteplase regimen has only been investigated with concomitant administration of heparin and aspirin as described in CLINICAL PHARMACOLOGY.

## ACTIVASE® (Alteplase)

- a. The bolus dose may be prepared in one of the following ways:
  1. By removing 15 mL from the vial of reconstituted (1 mg/mL) Activase using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the Activase vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
  2. By removing 15 mL from a port (second injection site) on the infusion line after the infusion set is primed.
  3. By programming an infusion pump to deliver a 15 mL (1 mg/mL) bolus at the initiation of the infusion.

b. The remainder of the Activase dose may be administered as follows:

- 50 mg vials**—administer using either a polyvinyl chloride bag or glass vial and infusion set.
- 100 mg vial**—insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted Activase. Hang the Activase vial from the plastic molded capping attached to the bottom of the vial.

### 3-Hour Infusion

The recommended dose is 100 mg administered as 60 mg in the first hour (of which 6 to 10 mg is administered as a bolus), 20 mg over the second hour, and 20 mg over the third hour. For smaller patients (< 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.<sup>15</sup>

Although the value of the use of anticoagulants during and following administration of Activase has not been fully studied, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients.

Aspirin and/or dipyridamole have been given to patients receiving Alteplase during and/or following heparin treatment.

a. The bolus dose may be prepared in one of the following ways:

1. By removing 6 to 10 mL from the vial of reconstituted (1 mg/mL) Activase using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the Activase vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
2. By removing 6 to 10 mL from a port (second injection site) on the infusion line after the infusion set is primed.
3. By programming an infusion pump to deliver a 6 to 10 mL (1 mg/mL) bolus at the initiation of the infusion.

b. The remainder of the Activase dose may be administered as follows:

- 50 mg vials**—administer using either a polyvinyl chloride bag or glass vial and infusion set.
- 100 mg vial**—insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted Activase. Hang the Activase vial from the plastic molded capping attached to the bottom of the vial.

### Acute Ischemic Stroke

#### THE TOTAL DOSE FOR TREATMENT OF ACUTE ISCHEMIC STROKE SHOULD NOT EXCEED 90 mg.

The recommended dose 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 bolus over 1 minute.

The safety and efficacy of this regimen with concomitant administration of heparin and aspirin during the first 24 hours after symptom onset has not been investigated.

a. The bolus dose may be prepared in one of the following ways:

1. By removing the appropriate volume from the vial of reconstituted (1 mg/mL) Activase using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the Activase vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
2. By removing the appropriate volume from a port (second injection site) on the infusion line after the infusion set is primed.
3. By programming an infusion pump to deliver the appropriate volume as a bolus at the initiation of the infusion.

b. The remainder of the Activase dose may be administered as follows:

- 50 mg vials**—administer using either a polyvinyl chloride bag or glass vial and infusion set.
- 100 mg vial**—remove from the vial any quantity of drug in excess of that specified for patient treatment. Insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted Activase. Hang the Activase vial from the plastic molded capping attached to the bottom of the vial.

### Pulmonary Embolism

The recommended dose is 100 mg administered by intravenous infusion over 2 hours. Heparin therapy should be instituted or reinstated near the end of or immediately following the Activase infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

The Activase dose may be administered as follows:

- 50 mg vials**—administer using either a polyvinyl chloride bag or glass vial and infusion set.
- 100 mg vial**—insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted Activase. Hang the Activase vial from the plastic molded capping attached to the bottom of the vial.

### Reconstitution and Dilution

Activase should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP, to the vial. It is important that Activase be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing Activase 1mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because Activase contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2–30°C (36–86°F). Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

Activase may be administered as reconstituted at 1 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass vials are acceptable. Activase is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP, or preservative-containing solutions for further dilution.

### 50 mg Vials

Reconstitution should be carried out using a large bore needle (e.g., 18 gauge) and a syringe, directing the stream of 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.

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

## ACTIVASE® (Alteplase)

### 100 mg Vial

Reconstitution should be carried out using the transfer device provided, adding the contents of the accompanying 100 mL vial of Sterile Water for Injection, USP, to the contents of the 100 mg vial of Activase powder. 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.**

### 100 mg VIAL RECONSTITUTION

1. Use aseptic technique throughout.
2. Remove the protective flip-caps from one vial of Activase and one vial of Sterile Water for Injection, USP (SWFI).
3. Open the package containing the transfer device by peeling the paper label off the package.
4. Remove the protective cap from one end of the transfer device and keeping the vial of SWFI upright, insert the piercing pin vertically into the center of the stopper of the vial of SWFI.
5. Remove the protective cap from the other end of the transfer device. **DO NOT INVERT THE VIAL OF SWFI.**
6. Holding the vial of Activase upside-down, position it so that the center of the stopper is directly over the exposed piercing pin of the transfer device.
7. Push the vial of Activase down so that the piercing pin is inserted through the center of the Activase vial stopper.
8. Invert the two vials so that the vial of Activase is on the bottom (upright) and the vial of SWFI is upside-down, allowing the SWFI to flow down through the transfer device. Allow the entire contents of the vial of SWFI to flow into the Activase vial (approximately 0.5 cc of SWFI will remain in the diluent vial). Approximately 2 minutes are required for this procedure.
9. Remove the transfer device and the empty SWFI vial from the Activase vial. Safely discard both the transfer device and the empty diluent vial according to institutional procedures.
10. Swirl gently to dissolve the Activase powder. **DO NOT SHAKE.**

**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 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 50242-044-13.

Each 100 mg Activase vial (58 million IU) is packaged with diluent for reconstitution (100 mL Sterile Water for Injection, USP), and one 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.

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