Indication
Activase (alteplase) is indicated for the treatment of acute ischemic stroke. Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment. Initiate treatment as soon as possible but within 3 hours after symptom onset.

Important Safety Information

Contraindications
Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit: current intracranial hemorrhage (ICH); subarachnoid hemorrhage; active internal bleeding; recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms); bleeding diathesis; and current severe uncontrolled hypertension.

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.
Data from parts 1 and 2 of the pivotal NINDS trial

NINDS was a 2-part randomized trial of Activase® (alteplase) vs placebo for the treatment of acute ischemic stroke. Part 1 (n=291) assessed changes in neurological deficits 24 hours after the onset of stroke. Part 2 (n=333) assessed if treatment with Activase resulted in clinical benefit at 3 months, defined as minimal or no disability using 4 stroke assessment.¹

In part 1, median baseline NIHSS score was 14 (min: 1; max: 37) for Activase- and 14 (min: 1; max: 32) for placebo-treated patients. In part 2, median baseline NIHSS score was 14 (min: 2; max: 37) for Activase- and 15 (min: 2; max: 33) for placebo-treated patients.

Patient identification required positive numerical assessment of NIHSS resulting in exclusion of patients with NIHSS of 0.²

### sICH INCIDENCE AT 36 HOURS*¹

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=312)</th>
<th>Activase (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>6.4</td>
<td></td>
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Of the 6.4% of Activase-treated patients who experienced an sICH within 36 hours, 45% (9/20) were fatal and 55% (11/20) were nonfatal.²

*sICH within 36 hours was defined as the occurrence of sudden neurological worsening followed by subsequent verification of intracranial hemorrhage through imaging.¹³

NIHSS=National Institutes of Health Stroke Scale; NINDS=National Institute of Neurological Disorders and Stroke.

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Important Safety Information

**Warnings and Precautions**

**Bleeding**

Activase can cause significant, and sometimes fatal internal or external bleeding. Avoid intramuscular injections and trauma to the patient. Perform venipunctures carefully and only as required. Fatal cases of hemorrhage associated with traumatic intubation in patients administered Activase have been reported. Heparin, aspirin, or Activase may cause bleeding complications; therefore carefully monitor for bleeding. If serious bleeding occurs, terminate the Activase infusion and treat appropriately.

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.
Data from a real-world analysis using the GWTG–Stroke registry

Retrospective analysis of 10,242 patients with acute ischemic stroke who received Activase within 3 hours of symptom onset from January 2009 to June 2010. Data were extracted from the Get With The Guidelines (GWTG)–Stroke registry.\textsuperscript{3}

Median baseline NIHSS score was 11 (interquartile range: 7–18). The number of patients stratified by NIHSS score were as follows: score of 0–5, 1875 (18.3%); score of 6–10, 2876 (28.1%); score of 11–15, 2146 (21.0%); score of 16–20, 1803 (17.6%); score of >20, 1542 (15.1%).\textsuperscript{3}

Patient identification utilized varying diagnostic methods resulting in inclusion of patients with NIHSS of 0.\textsuperscript{3}

\textbf{sICH INCIDENCE AT 36 HOURS**3}

\begin{center}
\begin{tikzpicture}
\begin{axis}[
    width=\textwidth,
    height=\textwidth,
    ybar stacked,\n    bar width=10,\n    ylabel=Patients (%),\n    xtick=data,\n    x tick label style={rotate=90,anchor=east},\n    nodes near coords,\n    nodes near coords align={anchor=west},\n]
\addplot coordinates{(0,2.2) (1,2.7) (2,4.6) (3,7.5) (4,9.3)};
\end{axis}
\end{tikzpicture}
\end{center}

\textsuperscript{**}A retrospective analysis using real-world evidence is observational in nature. These types of studies are more likely to contain inherent bias and confounding variables than a prospective clinical study, which limits the ability to draw conclusions about the causal effect of any particular factor or intervention. Limitations of this study are, patients and hospitals included may not be entirely representative, sICH was determined by a treating physician versus central review, and 11.3% of patients were excluded due to missing information. Study also showed additional variables that contribute to the overall risk for sICH in patients, including blood pressure, age, ethnicity, blood glucose, and gender.\textsuperscript{3}

Important Safety Information

\textbf{Warnings and Precautions (cont'd)}

\textit{Hypersensitivity}

Hypersensitivity, including urticarial/anaphylactic reactions have been reported. Rare fatal outcome for hypersensitivity was reported. Angioedema has been observed during and up to 2 hours after Activase infusion in patients treated for acute ischemic stroke and acute myocardial infarction. In many cases, patients received concomitant angiotensin converting enzyme inhibitors. Monitor patients during and for several hours after infusion for hypersensitivity. If signs of hypersensitivity occur, e.g. anaphylactoid reaction or angioedema develops, discontinue Activase and promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids, epinephrine).

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.
American Heart Association/American Stroke Association recommendations for Activase® (alteplase) treatment of patients with acute ischemic stroke

For severe stroke symptoms, intravenous (IV) alteplase is indicated within 3 hours from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms.\(^4\)

Class I; Level of Evidence B-R

For patients with mild but disabling stroke symptoms, IV alteplase is indicated within 3 hours from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms, in the opinion of the treating physician, from treatment with IV alteplase because there is proven clinical benefit for those patients.\(^4\)

Class I; Level of Evidence B-R

Important Safety Information

Warnings and Precautions (cont’d)

**Thromboembolism**

The use of thrombolytics can increase the risk of thrombo-embolic events in patients with high likelihood of left heart thrombus, such as patients with mitral stenosis or atrial fibrillation. Activase has not been shown to treat adequately underlying deep vein thrombosis in patients with PE. Consider the possible risk of re-embolization due to the lysis of underlying deep venous thrombi in this setting.

**Cholesterol Embolization**

Cholesterol embolism, sometimes fatal, has been reported rarely in patients treated with thrombolytic agents.

**Coagulation Tests May Be Unreliable During Activase Therapy**

Coagulation tests and/or measures of fibrinolytic activity may be unreliable during Activase therapy.

**Adverse Reactions**

The most frequent adverse reaction associated with Activase AIS therapy is bleeding.

Please see select Important Safety Information throughout and the accompanying full Prescribing Information.