Frequently asked questions about
Activase (Alteplase)
in acute ischemic stroke
What is Activase?
Activase® (Alteplase), also known as t-PA, is a tissue plasminogen activator produced by recombinant DNA technology. Activase belongs to the thrombolytic class of drugs and is the first drug to be indicated for the management of acute ischemic stroke. 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, as defined by the following indication and contraindications.

Please see accompanying full prescribing information for additional Important Safety Information.

What is the FDA-approved indication for Activase in stroke?
Activase 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 image method sensitive for the presence of hemorrhage.

Are there other thrombolytic agents I can use to treat acute ischemic stroke?
Activase is the only FDA-approved medication indicated for the treatment of acute ischemic stroke. It was approved for this indication in 1996.

How does Activase work?
Activase is an enzyme produced by recombinant DNA technology. When introduced into the systemic circulation, Activase:

- Binds to the fibrin protein threads of a thrombus
- Converts the enmeshed plasminogen to plasmin, initiating local fibrinolysis
- Produces limited conversion of plasminogen in the absence of fibrin, thus causing a limited systemic effect

The net physiologic effect of Activase is to dissolve clots so that blood flow can be restored and viable tissue may be reperfused.

Please see accompanying full prescribing information for additional Important Safety Information.
In what types of patients is the use of Activase contraindicated?

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 (eg, >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 (eg, 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 an elevated activated partial thromboplastin time (aPTT) at presentation
  - Platelet count <100,000/mm³
What is the efficacy profile of Activase?

In the NINDS* pivotal trial, 30% more patients had favorable outcomes with Activase at 3 months.†

- There was an 11% to 13% absolute increase in favorable outcomes at 3 months for patients treated with Activase vs patients given placebo.
  - This was seen across 4 assessment scales including the National Institutes of Health Stroke Scale (NIHSS), Barthel Index, Modified Rankin Scale, and Glasgow Outcome Scale.

- The NINDS trial did not study patients presenting 3 or more hours after acute ischemic stroke symptom onset or patients with minor or rapidly improving stroke symptoms.

*NIHSS=National Institute of Neurological Disorders and Stroke.

Part 2 of a randomized, double-blind, placebo-controlled study (N=333) conducted by NINDS of patients at 3 months after being treated for ischemic stroke with intravenous recombinant tissue plasminogen activator (n=168) or placebo (n=165) within 3 hours of onset.

†NINDS was a 2-part study. In part 1 (n=291), the clinical activity of t-PA was evaluated, as indicated by an improvement of 4 points over baseline National Institutes of Health Stroke Scale (NIHSS) scores, or the resolution of the neurologic deficit within 24 hours of stroke symptom onset. Part 2 of NINDS (n=333 patients) used a global test statistic to assess clinical outcome at 3 months, based on scores on the NIHSS, Barthel Index, Modified Rankin Scale, and Glasgow Outcome Scale.

Favorable outcome=NIHSS, <1; Barthel, 95 or 100; Modified Rankin, 0 or 1; Glasgow, 1. P value is based on a global scale.
Are the benefits of Activase sustained beyond 3 months?

The benefits of thrombolytic therapy vs placebo were sustained at 1 year.²

- There was an 11% to 13% absolute increase in the number of patients with minimal or no disability among patients treated with Activase, as observed across 3 assessment scales

- There was a 12% absolute (32% relative) increase in the number of patients receiving Activase with minimal or no disability based on a score of 95 or 100 on the Barthel Index; a 13% absolute (46% relative) increase in the number of patients with minimal or no disability based on a score of 0 or 1 on the Modified Rankin Scale; and an 11% absolute (34% relative) increase in the number of patients with minimal or no disability based on a score of 1 on the Glasgow Outcome Scale


Note: NIHSS scores were unavailable at 6 and 12 months because follow-up assessments were conducted by telephone. Favorable outcome=Barthel, 95 or 100; Modified Rankin, 0 or 1; Glasgow, 1.

A 1-year follow-up study of outcome data for the 624 patients enrolled in the original 2-part NINDS study, using intent-to-treat analysis (26 patients missing at 12-month assessment considered to have unfavorable outcomes). There were 312 patients in each group, including those treated with t-PA for ischemic stroke.

A favorable outcome was defined as minimal or no disability as measured by the Barthel Index, the Modified Rankin Scale, and the Glasgow Outcome Scale.

What is the safety profile of Activase?

The results of the NINDS pivotal trial showed\(^1\):

- **6.4% incidence of symptomatic intracranial hemorrhage (SICH) within the first 36 hours**
  - Significantly higher than among patients treated with placebo (0.6%, \(P<0.001\))
  - Activase was associated with a significantly higher rate of SICH than placebo; it did not result in an increased rate of severe disability or death
  - Approximately half, or 55%, of the patients experiencing SICH had nonfatal outcomes at 36 hours (11 of 20 patients had nonfatal outcomes, 9 had fatal outcomes)

- No statistically significant difference in mortality at 90 days
  - 17% mortality among patients treated with Activase vs 21% among patients receiving placebo

The results from a meta-analysis of SICH in 15 published, open-label studies (N>2600) of Activase are shown below\(^1,3-6\):

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>6.4</td>
</tr>
<tr>
<td>CASES</td>
<td>4.6</td>
</tr>
<tr>
<td>STARS</td>
<td>3.3</td>
</tr>
<tr>
<td>Houston</td>
<td>4.5</td>
</tr>
<tr>
<td>Cologne</td>
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<tr>
<td>Berlin</td>
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<tr>
<td>Cleveland (2000)</td>
<td>15.7</td>
</tr>
<tr>
<td>Cleveland CCHS (2000)</td>
<td>13.4</td>
</tr>
<tr>
<td>Cleveland CCHS (2003)(^\d)</td>
<td>6.4</td>
</tr>
<tr>
<td>Calgary</td>
<td>8.8</td>
</tr>
<tr>
<td>OSF Stroke Network</td>
<td>5.3</td>
</tr>
<tr>
<td>Mercy/Sacramento</td>
<td>7.0</td>
</tr>
<tr>
<td>Oregon</td>
<td>9.1</td>
</tr>
<tr>
<td>t-PA Stroke Survey(^\d)</td>
<td>5.8</td>
</tr>
<tr>
<td>Connecticut(^\d)</td>
<td>6.3</td>
</tr>
<tr>
<td>Indianapolis(^\d)</td>
<td>8.0</td>
</tr>
<tr>
<td>Michigan(^\d)</td>
<td>10.8</td>
</tr>
<tr>
<td>ABOVE STUDIES</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Adapted from Graham GD. *Stroke*. 2003;34:2847; Katzan IL, et al. *Stroke*. 2003;34:799-800. The Cleveland (2000) study evaluated 29 area hospitals. Cleveland Clinic Health System (CCHS) studies later evaluated a subset of 9 hospitals. The NINDS and CCHS results are not factored into the overall 5.2% rate of SICH in “ABOVE STUDIES.”

\(*\) SICH percentages are for bleeding within the first 36 hours or the closest reported time point.

\(\d\) Indicates retrospective study; all others were prospective.

Please see accompanying full prescribing information for additional Important Safety Information.
The Cleveland Clinic Health System Experience:
- Protocol violations were reduced by nearly half
- There was a 6.4% incidence of SICH, identical to that found in NINDS


1One tertiary care center and 8 community hospitals.

2Protocol deviations included: t-PA treatment given beyond 3 hours (n=7), antiplatelet agents or anticoagulant given within 24 hours (n=1), and deviations from blood pressure guidelines (n=3). t-PA administration was across all admitted ischemic stroke patients.

The risks of Activase therapy in the treatment of acute ischemic stroke may be increased in the following conditions:
- Patients with severe neurologic deficit (eg, NIHSS score >22) at presentation; there is an increased risk of intracranial hemorrhage in these patients
- Patients with major early infarct signs on a CT scan (eg, substantial edema, mass effect, or midline shift)

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How is Activase dosed for acute ischemic stroke?

The recommended dose is 0.9 mg/kg (not to exceed 90 mg total dose). Ten percent of the total dose is administered as an initial intravenous bolus dose over 1 minute. The remainder of the dose should be infused over 60 minutes.

How is Activase reconstituted?

Activase should be reconstituted immediately before use and only by aseptically adding Sterile Water for Injection (SWFI), USP. This preparation will result in a colorless to pale yellow transparent solution containing Activase 1 mg/mL.

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. When diluting, either polyvinyl chloride bags or glass vials are acceptable.

Reconstitution of 100-mg vials

Reconstitution should be carried out using the transfer device provided and adding the contents of the 100-mg vial of SWFI to the contents of the 100-mg Activase powder.

1. Wipe the tops of the SWFI vial and 100-mg vial of Activase with alcohol to reduce the risk of contamination.

2. 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.

3. Remove the protective cap from the other end of the transfer device. DO NOT INVERT THE VIAL OF SWFI.

4. 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.

5. Push the vial of Activase down so that the piercing pin is inserted through the center of the Activase vial stopper.

Please see accompanying full prescribing information for additional Important Safety Information.
6. Invert the 2 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 mL of SWFI will remain in the diluent vial). Approximately 2 minutes are required for this procedure.

7. 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.

8. Mix with a gentle swirl or slow inversion. DO NOT SHAKE. Slight foaming upon reconstitution is not unusual. Allow the solution to stand undisturbed for several minutes to allow any large bubbles to dissipate. Activase is stable for up to 8 hours in these solutions at room temperature. No other medication should be added to infusion solutions containing Activase. Any unused infusion solution should be discarded.
Reconstitution of 50-mg vials

1. Wipe the tops of the SWFI vial and 50-mg vial of Activase with alcohol to reduce the risk of contamination.

2. Withdraw 50 mL of SWFI. Diluent is included. DO NOT USE Bacteriostatic Water for Injection, USP.

3. Inject the 50 mL of SWFI into the 50-mg Activase vial, using a large bore needle (eg, 18-gauge) and a syringe, directing the stream into the lyophilized cake. DO NOT USE IF VACUUM IS NOT PRESENT. The syringe should not be primed with air during preparation and should be inserted into the Activase vial stopper. Slight foaming upon reconstitution is not unusual. Allow the solution to stand undisturbed for several minutes to allow any large bubbles to dissipate.

4. Mix with a gentle swirl or slow inversion. DO NOT SHAKE. No other medications should be added to infusion solutions containing Activase.

Before administration, the Activase solution should be visually inspected for particulate matter and discoloration.

Please see accompanying full prescribing information for additional Important Safety Information.
How is the bolus dose of Activase administered?

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

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

3. Administer bolus
   Administer initial IV bolus over 1 minute.
How is the remainder of the Activase dose administered?

Infuse the remaining 90% of the 0.9 mg/kg dose over 60 minutes.

100-mg vials – 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 vial from the plastic molded capping attached to the bottom of the vial.

Activase can also be administered by programming an infusion pump. Remember to prime the IV pump tubing with the Activase solution so that the infusion begins immediately following the bolus dose.

Because IV pumps and tubing vary, a standardized procedure should be initiated at each hospital to ensure delivery of the full Activase dose, including the volume of Activase in the IV tubing. One possible solution is to spike a small bag (eg, 50 mL) of 0.9% sodium chloride injection, USP, with the end of the Activase infusion set when the Activase vial is empty. The infusion should continue at the same rate to ensure that all the Activase remaining in the tubing is received by the patient.

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

50-mg vials – Administer using either a polyvinyl chloride bag or glass vial and infusion set.

For specifics regarding dosing and administration, please see the Activase full prescribing information.

What should be monitored in the first 24 hours after Activase therapy is administered? \(^{5,6}\)

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 checklist on the following page as a guide in tracking your patients’ needs.
Activase postcare checklist

☐ Perform neurologic assessments to monitor for neurologic deterioration. It is recommended that a full NIHSS assessment be performed on a patient upon admission.

٠ Every 15 minutes during infusion
٠ Every 30 minutes for 6 hours after infusion
٠ Hourly until 24 hours after infusion

☐ 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
٠ Arterial and venous punctures should be minimized and checked frequently

☐ Measure blood pressure.
٠ Every 15 minutes for the first 2 hours after infusion
٠ Every 30 minutes for the next 6 hours after infusion
٠ Hourly until 24 hours after 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.

☐ 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.

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

— Adapted from the 2007 AHA/ASA guidelines.

If any of the above occur, immediately inform the attending physician or neurologist.
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
Activase therapy in patients with AIS is contraindicated in certain situations (eg, suspicion of subarachnoid hemorrhage on pretreatment evaluation), recent (within 3 months) intracranial or intraspinal surgery, history of intracranial hemorrhage, uncontrolled hypertension at time of treatment, active internal bleeding, known bleeding diathesis (eg, current use of oral anticoagulants, administration of heparin within 48 hours of onset of stroke, platelet count <100,000) (see CONTRAINDICATIONS for full list).

The most common complication during Activase therapy is bleeding. Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, Activase therapy should be discontinued immediately. Death and permanent disability are not uncommonly reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

The risks of Activase therapy may be increased and should be weighed against the anticipated benefits in certain conditions.

[See WARNINGS in full prescribing information.]

- Patients with severe neurological deficit (eg, 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 (eg, substantial edema, mass effect, or midline shift).

Treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.

Oroolingual angioedema has been observed in postmarketing experience in patients treated with Activase for AIS. Patients should be monitored during and for several hours after infusion for signs of orolingual angioedema.

Please see full prescribing information for additional Important Safety Information.
Activase is supplied in 2 convenient quantities.

Activase 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.