ACTIVASE®
ALTEPLASE
A RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

DOSING & ADMINISTRATION GUIDE FOR ACUTE ISCHEMIC STROKE

Indication

Activase® (alteplase) is indicated for the treatment of acute ischemic stroke (AIS). 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 additional Important Safety Information on pages 13 & 14 and the full Prescribing Information.

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A Step-by-Step Guide to Administering Activase

Includes instructions on:

Reconstitution

Proper preparation of Activase 100-mg solution for infusion

Administration

Infusion of the initial bolus and full Activase dose for Acute Ischemic Stroke

Dosing table

Find the correct Activase dose for your appropriate Acute Ischemic Stroke patient

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

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Activase 100-mg Reconstitution[1]

Supplies

The Activase 100-mg kit includes:

- Activase 100-mg vial.
- 100-mL vial of Sterile Water for Injection (SWFI), USP.
- Transfer device.
- Instructions for Use of 100-mg Activase.
- Full Prescribing Information.

Activase is for intravenous administration only. Extravasation of Activase infusion can cause ecchymosis or inflammation. If extravasation occurs, terminate the infusion at the IV site and apply local therapy.

Store lyophilized Activase at controlled room temperature not to exceed 30° C (86° F), or under refrigeration at 2° to 8° C (36° to 46° F). Protect the lyophilized material during extended storage from excessive exposure to light.

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

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Activase 100-mg Reconstitution[1]

Reconstitution Overview

- Use only the accompanying SWFI, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP.
- Reconstitute using aseptic technique.
- Slight foaming is not unusual; let stand undisturbed for several minutes to allow large bubbles to dissipate. Inspect parenteral drug products for particulate matter and discoloration (solution should be colorless to pale yellow and transparent) prior to administration.
- Activase may be administered as reconstituted at 1 mg/mL or further diluted 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, using either polyvinyl chloride bags or glass vials.
- Avoid excessive agitation during dilution; mix by gently swirling and/or slow inversion.
- Activase contains no antibacterial preservatives and must be used within 8 hours following reconstitution (when stored at 2-30° C).

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

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Activase 100-mg Reconstitution[1]

Getting Started

Follow your institution's policy for aseptic technique when preparing Activase.

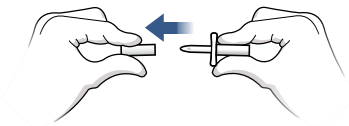
Step 1
UNCAP VIALS

Uncap Activase and SWFI vials.

Step 2
WIPE VIAL TOPS

Wipe each stopper with a separate alcohol swab.

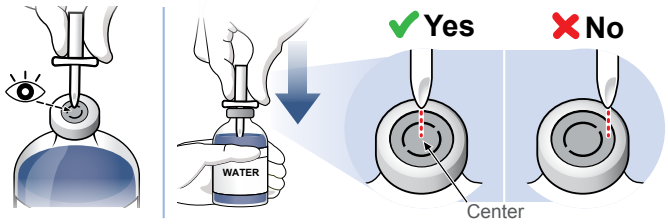
Step 3
REMOVE TRANSFER DEVICE



Remove transfer device from packaging, then remove one protective cap. **Do not wipe transfer device spikes with alcohol.**

Note: Either side of transfer device can be used.

Step 4
SPIKE STERILE WATER



Keeping the SWFI bottle upright, insert transfer device into sterile water vial **straight down** through **stopper's center ring**.

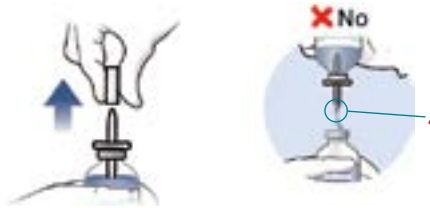
⚠ **Do not invert water vial yet.**

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

Activase 100-mg Reconstitution[1]

Combining the Vials

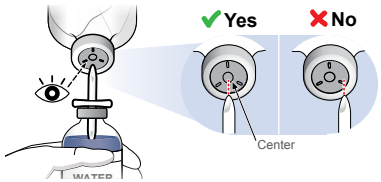
Step 5
REMOVE PROTECTIVE CAP



Remove protective cap from other end of transfer device.

⚠ Do not invert water vial yet. Inverting too early may lead to leakage and incorrect dosing.

Step 6
POSITION ACTIVASE VIAL



Hold Activase vial upside down over spike.

Position the center of the Activase stopper over the exposed pin of the transfer device.

Step 7
SPIKE ACTIVASE VIAL

Press Activase vial down to insert spike straight through center of Activase vial stopper.

⚠ Inserting the spike off-center could lead to stopper collapse.

Step 8
FLIP VIALS

Flip vials so Activase vial is on bottom (upright) and SWFI vial is upside down. Wait until sterile water is done flowing into Activase vial.

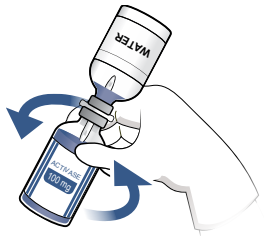
If the flow does not start immediately or pauses, initiate the flow by flipping and re-inverting the vials.

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

Activase 100-mg Reconstitution[1]

Mixing the Solution

Step 9
GENTLY SWIRL ACTIVASE



Gently swirl and/or invert Activase vial slowly to dissolve powder.

⚠ **Do not shake vials. Shaking may lead to excessive foaming and degraded medication.**

Step 10
REMOVE WATER VIAL

Remove and discard sterile water vial and transfer device. Let stand until bubbles disappear.

Step 11
INSPECT SOLUTION

Reconstituted Activase vial (1 mg/mL) should be colorless to pale yellow, transparent, and free of particulates. If needed, let stand undisturbed for a few minutes to allow large bubbles to dissipate.

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Activase Dosing and Administration for Acute Ischemic Stroke[1]

Dosing Overview

- **Administer Activase as soon as possible but within 3 hours after onset of symptoms.**
- The recommended dose is 0.9 mg/kg **(not to exceed 90 mg total dose)**, with 10% of the total dose administered as an initial intravenous bolus over 1 minute and the remainder infused over 60 minutes.
- **The dose of treatment of acute ischemic stroke should not exceed 90 mg.**
- Immediately following the bolus dose, infuse the remaining 90% of the 0.9 mg/kg dose over 60 minutes. To ensure the full dose is delivered, it may be necessary to clear the line, following your hospital's protocols. One example may be to spike a small bag (for example 100 mL of 0.9% sodium chloride USP) at the end of the Activase infusion set when the vial is empty and continue the infusion at the same rate to ensure the full dose is administered.
- During and following Activase administration for the treatment of acute ischemic stroke, frequently monitor and control blood pressure.
- In patients without recent use of oral anticoagulants or heparin, Activase treatment can be initiated prior to the availability of coagulation study results. Discontinue Activase if the pretreatment International Normalized Ratio is greater than 1.7 or the activated partial thromboplastin time is elevated.

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

Activase Dosing and Administration for Acute Ischemic Stroke[1,2]

Preparing the Dose

Activase is for intravenous administration only. Do not add any other medication to infusion solutions containing Activase. Extravasation of Activase infusion can cause ecchymosis or inflammation. If extravasation occurs, terminate the infusion at the IV site and apply local therapy. See full prescribing information for alternative dilution instructions.

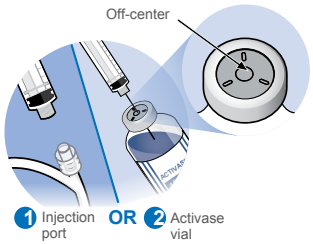
Administration Warning: Review important information below before continuing.

- Do not push air from the syringe into the vial. The vial is not under vacuum and adding air at any time may result in leakage and incorrect dosing.
- Only insert needles within center ring of stopper, away from the hole made by transfer device when withdrawing medication to avoid leakage and incorrect dosing. Do not insert needles outside of the center ring of stopper.

Step 1
INSPECT SOLUTION

After reconstitution to 1 mg/mL, inspect the solution for particulate matter and discoloration prior to administration. The reconstituted preparation results in a colorless to pale yellow transparent solution that is free of particulates.

Step 2
PREPARE BOLUS



DO NOT prime syringe

The bolus dose is 10% of the 0.9-mg/kg dose. Prepare it one of the following ways:

50-mg vials

Using a large bore needle and a syringe, reconstitute by adding the contents of the accompanying 50-mL vial of SWFI to the 50-mg vial of Activase, directing the SWFI stream into the lyophilized cake. **Do not use if vacuum is not present.**

Remove the appropriate dose using a syringe and needle. The syringe should not be primed with air;

OR

100-mg vials

Check if bolus is needed. If yes, attach needle to an empty Luer syringe. Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw the bolus amount.

Alternative option

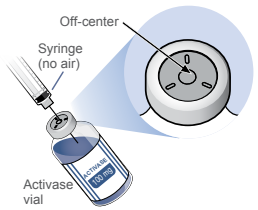
The bolus may also be left in the vial and administered via an infusion pump or removed from a port on the infusion line.

⚠ Do not push any air from syringe into vial (may cause leakage).

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

Activase Dosing and Administration for Acute Ischemic Stroke[1,2]

Step 3
PREPARE INFUSION



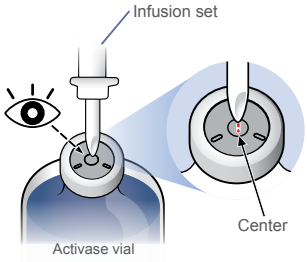
⚠ **Do not push any air from syringe into vial (may cause leakage).**

50-mg vials
Withdraw the appropriate dose from the vial and inject it into a polyvinyl chloride bag or glass vial.

100-mg vials
Check if there is excess volume in the vial. If yes, attach needle to an empty Luer syringe. Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw the excess volume. Discard any excess volume. Leave infusion dose in vial.

Infusing Activase

Step 4
PREPARE INFUSION SET



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

100-mg vials
- Insert spike from IV tubing set into center of vial stopper, through same hole made by transfer device.

⚠ **Do not make a new hole in the vial stopper. Additional holes in vial stopper may lead to leakage.**

- Peel the clear plastic hanger from the vial label. Hang the Activase vial from the resulting loop.

Step 5
PRIME INFUSION SET

Prime infusion set tubing with Activase solution.

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

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Activase Dosing and Administration for Acute Ischemic Stroke[1,2]

Step 6
ADMINISTER BOLUS

Administer initial IV bolus over 1 minute.

Administer IV bolus directly through the IV port or program the infusion pump to deliver the bolus dose.

Step 7
ADMINISTER REMAINDER AND CLEAR IV TUBING

Immediately following the bolus dose, infuse the remaining 90% of the 0.9-mg/kg dose. When the Activase vial is empty, ensure the full dose is delivered by clearing the line according to your hospital's protocol. One example may be to spike a small bag (for example 100mL of 0.9% sodium chloride USP) at the end of the Activase infusion set when the vial is empty and continue the infusion at the same rate to ensure the full dose is administered. Any unused infusion solution should be discarded.

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Activase Dosing

Dosing Tables

Weight (kg)	Total Dose	Discard Quantity*	Bolus Dose (over 1 minute)	Infusion Dose (over 60 minutes)
40.9	36.8	63.2	3.7	33.1
41.8	37.6	62.4	3.8	33.8
42.7	38.4	61.6	3.8	34.6
43.6	39.2	60.8	3.9	35.3
44.5	40.1	59.9	4.0	36.1
45.5	41.0	59.0	4.1	36.9
46.4	41.8	58.2	4.2	37.6
47.3	42.6	57.4	4.3	38.3
48.2	43.4	56.6	4.3	39.1
49.1	44.2	55.8	4.4	39.8
50.0	45.0	55.0	4.5	40.5
50.9	45.8	54.2	4.6	41.2
51.8	46.6	53.4	4.7	41.9
52.7	47.4	52.6	4.7	42.7
53.6	48.2	51.8	4.8	43.4
54.6	49.1	50.9	4.9	44.2
55.5	50.0	50.0	5.0	45.0
56.4	50.8	49.2	5.1	45.7
57.3	51.6	48.4	5.2	46.4
58.2	52.4	47.6	5.2	47.2
59.1	53.2	46.8	5.3	47.9
60.0	54.0	46.0	5.4	48.6

Weight (kg)	Total Dose	Discard Quantity*	Bolus Dose (over 1 minute)	Infusion Dose (over 60 minutes)
60.9	54.8	45.2	5.5	49.3
61.8	55.6	44.4	5.6	50.0
62.7	56.4	43.6	5.6	50.8
63.6	57.2	42.8	5.7	51.5
64.5	58.1	41.9	5.8	52.3
65.5	59.0	41.0	5.9	53.1
66.4	59.8	40.2	6.0	53.8
67.3	60.6	39.4	6.1	54.5
68.2	61.4	38.6	6.1	55.3
69.1	62.2	37.8	6.2	56.0
70.0	63.0	37.0	6.3	56.7
70.9	63.8	36.2	6.4	57.4
71.8	64.6	35.4	6.5	58.1
72.7	65.4	34.6	6.5	58.9
73.6	66.2	33.8	6.6	59.6
74.5	67.1	32.9	6.7	60.4
75.5	68.0	32.0	6.8	61.2
76.4	68.8	31.2	6.9	61.9
77.3	69.6	30.4	7.0	62.6
78.2	70.4	29.6	7.0	63.4
79.1	71.2	28.8	7.1	64.1
80.0	72.0	28.0	7.2	64.8

Weight (kg)	Total Dose	Discard Quantity*	Bolus Dose (over 1 minute)	Infusion Dose (over 60 minutes)
80.9	72.8	27.2	7.3	65.5
81.8	73.6	26.4	7.4	66.2
82.7	74.4	25.6	7.4	67.0
83.6	75.2	24.8	7.5	67.7
84.5	76.1	23.9	7.6	68.5
85.5	77.0	23.0	7.7	69.3
86.4	77.8	22.2	7.8	70.0
87.3	78.6	21.4	7.9	70.7
88.2	79.4	20.6	7.9	71.5
89.1	80.2	19.8	8.0	72.2
90.0	81.0	19.0	8.1	72.9
90.9	81.8	18.2	8.2	73.6
91.8	82.6	17.4	8.3	74.3
92.7	83.4	16.6	8.3	75.1
93.6	84.2	15.8	8.4	75.8
94.5	85.1	14.9	8.5	76.6
95.5	86.0	14.0	8.6	77.4
96.4	86.8	13.2	8.7	78.1
97.3	87.6	12.4	8.8	78.8
98.2	88.4	11.6	8.8	79.6
99.1	89.2	10.8	8.9	80.3
≥100.0	90.0	10.0	9.0	81.0

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Important Safety Information

Indication

Activase® (alteplase) is indicated for the treatment of acute ischemic stroke (AIS). 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.

Warnings and Precautions

Bleeding

Activase can cause significant, sometimes fatal internal or external bleeding, especially at arterial and venous puncture sites. 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. The concomitant administration of heparin and aspirin with and following infusions of Activase for the treatment of AIS during the first 24 hours after symptom onset has not been investigated. Because heparin, aspirin, or Activase may cause bleeding complications, carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of Activase, while patients are still receiving anticoagulant therapy. If serious bleeding occurs, terminate the Activase infusion, and treat properly.

In the following conditions, the risks of bleeding with Activase are increased and should be weighed against the anticipated benefits: recent major surgery or procedure; cerebrovascular disease; recent intracranial hemorrhage; recent gastrointestinal or genitourinary bleeding; recent trauma; hypertension; 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; and patients currently receiving oral anticoagulants, or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

Important Safety Information (cont.)

Warnings and Precautions (cont.)

Hypersensitivity

Hypersensitivity, including urticarial / anaphylactic reactions, have been reported after administration of Activase. Rare fatal outcome for hypersensitivity was reported. Angioedema has been observed during and up to 2 hours after 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 the Activase infusion and promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids, epinephrine).

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; the true incidence is unknown. It is associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy.

Coagulation Tests May be Unreliable during Activase Therapy

Coagulation tests and/or measures of fibrinolytic activity may be unreliable during Activase therapy unless specific precautions are taken to prevent in vitro artifacts. When present in blood at pharmacologic concentrations, Activase remains active under *in vitro* conditions, which can result in degradation of fibrinogen in blood samples removed for analysis.

Adverse Reactions

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

Please see the full Prescribing Information for additional Important Safety Information and Instructions for Use.

References: 1. Activase [prescribing information]. South San Francisco, CA. Genentech, Inc. **2.** Dear Pharmacist letter, sent May 17, 2018. Genentech, Inc. South San Francisco, CA.

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