

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrACTIVASE® rt-PA

alteplase for injection

Lyophilized Powder for Injection - 50 mg and 100 mg
Fibrinolytic Agent

ACUTE ISCHEMIC STROKE INDICATION ONLY

Hoffmann-La Roche Limited
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L5N 5M8

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.3 Reconstitution	XX/XXXX
4 Dosage and Administration, 4.4 Administration	XX/XXXX

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics	4
1.2 Geriatrics	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	5
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations	5
4.2 Recommended Dose and Dosage Adjustment	6
4.3 Reconstitution	6
4.4 Administration	10
5 OVERDOSAGE	12
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	13
7 WARNINGS AND PRECAUTIONS	14
7.1 Special Populations	17
7.1.1 Pregnant Women	17
7.1.2 Breast-feeding	17
7.1.3 Pediatrics	17
7.1.4 Geriatrics	17
8 ADVERSE REACTIONS	17
8.1 Adverse Reaction Overview	17
8.2 Clinical Trial Adverse Reactions	18
8.3 Less Common Clinical Trial Adverse Reactions	19

8.4	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	19
8.5	Post-Market Adverse Reactions.....	19
9	DRUG INTERACTIONS.....	20
9.1	Serious Drug Interactions	20
9.2	Drug Interactions Overview	20
9.3	Drug-Behavioural Interactions.....	20
9.4	Drug-Drug Interactions	20
10	CLINICAL PHARMACOLOGY	20
10.1	Mechanism of Action	20
10.2	Pharmacodynamics.....	20
10.3	Pharmacokinetics.....	20
11	STORAGE, STABILITY AND DISPOSAL	20
12	SPECIAL HANDLING INSTRUCTIONS.....	21
PART II: SCIENTIFIC INFORMATION		21
13	PHARMACEUTICAL INFORMATION.....	21
14	CLINICAL TRIALS	23
14.1	Trial Design and Study Demographics	23
14.2	Study Results.....	24
15	MICROBIOLOGY	25
16	NON-CLINICAL TOXICOLOGY	25
PATIENT MEDICATION INFORMATION.....		27

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACTIVASE rt-PA (alteplase for injection) is indicated for:

- The management of **acute ischemic stroke** (AIS) 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. Eligibility criteria of the National Institute of Neurological Disorders and Stroke (NINDS) protocol must be strictly adhered to (see 2 CONTRAINDICATIONS).
- Patients should be advised of the potential risk as well as the benefits of the use of ACTIVASE rt-PA for this indication.

For information on use in acute myocardial infarction (AMI), please consult the product monograph for the AMI indication.

1.1 Pediatrics

- Pediatrics (<18 years of age): Safety and effectiveness of ACTIVASE rt-PA in children (age less than 18 years) has not been established. Therefore, treatment of such patients is not recommended.

1.2 Geriatrics

- Geriatrics (>77 years of age): Evidence from clinical studies and experience suggests that risks of therapy may be increased in the elderly. In ACTIVASE rt-PA treated patients (NINDS study) of advanced age (e.g. >77 years of age), the trend toward increased risk for symptomatic ICH within the first 36 hours was more prominent. Similar trends were also seen for total ICH and for all-cause 90-day mortality. Analyses for efficacy suggested a reduced but still favourable clinical outcome for these patients.

2 CONTRAINDICATIONS

ACTIVASE rt-PA (alteplase for injection) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

ACTIVASE rt-PA (alteplase for injection) therapy is contraindicated in the following situations because of an increased risk of bleeding, which could result in significant disability or death:

- Symptom onset greater than 3 hours
- Evidence of intracranial hemorrhage on pretreatment evaluation
- Suspicion of subarachnoid hemorrhage on pretreatment evaluation
- Recent intracranial surgery or intraspinal surgery, serious head trauma or previous stroke (within 3 months)
- History of intracranial hemorrhage

- Uncontrolled hypertension at time of treatment (e.g., > 185 mm Hg systolic or >110 mm Hg diastolic)
- Aggressive treatment required to reduce blood pressure to specified limits
- Seizure at the onset of stroke
- Active internal bleeding
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Major surgery within 14 days
- Gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days
- Arterial puncture at a noncompressible site within the previous 7 days
- Blood glucose < 3 or > 22 mmol/L (<50 mg/dL or >400 mg/dL)
- Recent myocardial infarction (<3 months) and/or clinical presentation associated with post-myocardial infarction pericarditis
- 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 an elevated activated partial thromboplastin time (aPTT) at presentation
 - Platelet count < 100,000/mm³

The safety and efficacy of treatment with ACTIVASE rt-PA in patients with minor neurological deficit or with rapidly improving symptoms prior to the start of ACTIVASE rt-PA administration has not been evaluated. **Therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.**

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- ACTIVASE rt-PA is a drug known to cause severe bleeding and an increased incidence of intracranial hemorrhage (See 7 WARNINGS AND PRECAUTIONS). Use of ACTIVASE rt-PA for the treatment of stroke is limited to physicians experienced in acute stroke management, who are treating patients in a hospital setting equipped with appropriate laboratory facilities to follow the neurological (CT scan) and hematological status of the patient.
- Eligibility criteria of the National Institute of Neurological Disorders and Stroke (NINDS) protocol must be strictly adhered to (see 1 INDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

ACTIVASE rt-PA (alteplase for injection) is intended for intravenous use only. It should be given via a dedicated intravenous line with an infusion pump. Extravasation of ACTIVASE rt-PA infusion can cause ecchymosis and/or inflammation. Management consists of terminating the infusion at the IV site and application of local therapy.

Blood pressure should be monitored frequently and controlled during and following administration of

ACTIVASE rt-PA 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.

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. The concomitant use of heparin or acetylsalicylic acid 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 rt-PA for the management of acute ischemic stroke is unknown (See 7 WARNINGS AND PRECAUTIONS).

THE DOSE FOR TREATMENT OF ACUTE ISCHEMIC STROKE SHOULD NOT EXCEED 90 MG.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose is 0.9 mg/kg (maximum of 90 mg) infused over 60-minutes with 10% of the total dose administered as an initial intravenous bolus over 1 minute. The recommended total dose is based upon patient weight.

4.3 Reconstitution

The reconstituted solution may be diluted further immediately before administration to yield concentrations as low as 0.5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. 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.

No other medication should be added to ACTIVASE rt-PA solution. Solutions should be administered as described above. Unused infusion solution should be immediately discarded.

50 MG VIALS

ACTIVASE rt-PA should be reconstituted by aseptically adding to the vial of ACTIVASE rt-PA, the appropriate volume of Sterile Water for Injection, USP [SWFI] (50 mL for 50 mg vials, 100 mL for 100 mg vials).

It is important that ACTIVASE rt-PA be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection.

The reconstituted preparation results in a colourless to pale yellow transparent solution containing ACTIVASE rt-PA 1.0 mg/mL at a pH of 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

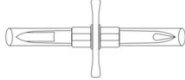

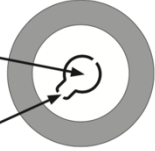

Before further dilution or administration, parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. Activase contains no antibacterial preservatives and must be used within 8 hours following reconstitution (when stored 2–30°C). (see 11 STORAGE, STABILITY AND DISPOSAL).

Do not use a transfer device but use a large bore needle (e.g. 18 gauge), **and the accompanying 50 mL Sterile Water for Injection, USP**, direct 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

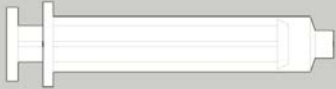
unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. Excessive or vigorous shaking should be avoided.


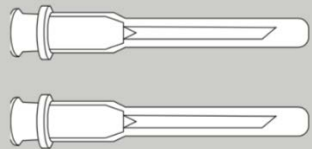

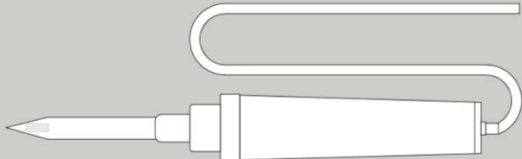
100 MG VIALS

Activase 100 mg Kit Contents

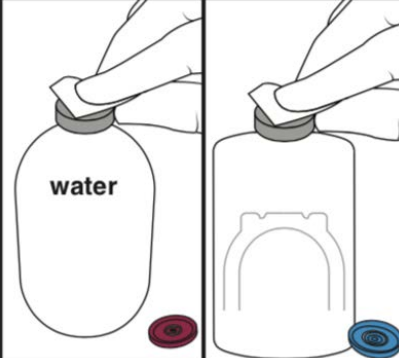
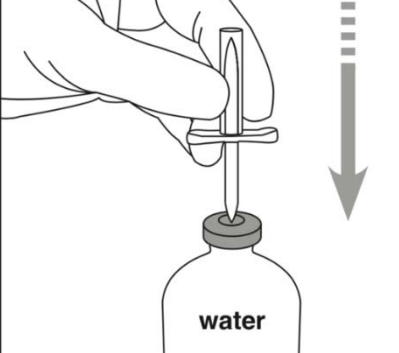
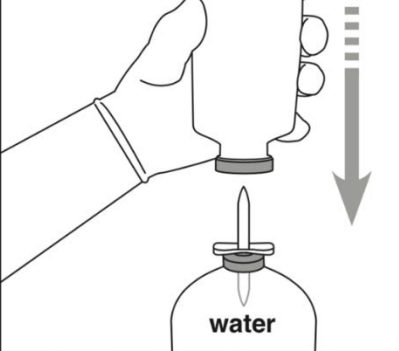
Transfer device	
Activase 100 mg vial (no vacuum)	
Activase 100 mg vial stopper parts:	
Sterile Water for Injection (water) vial Note: Do not use Bacteriostatic Water for Injection, USP.	
Prescribing Information	
Instructions for Use	

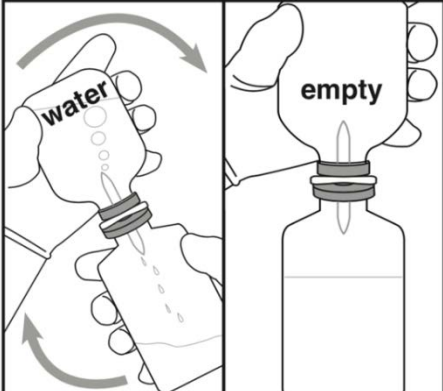
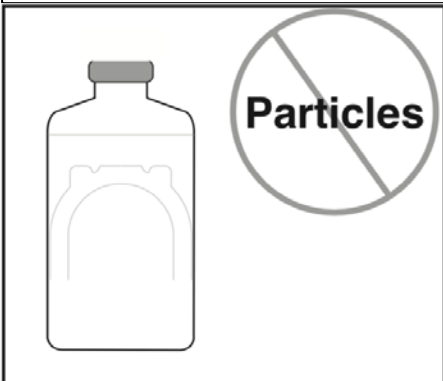
Activase 100 mg Also Required (not included in kit)

1 Luer syringe for removing bolus dose, as needed	
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1 Luer syringe for removing excess volume, as needed	
2 large bore needles	
2 Alcohol swabs	
IV infusion set	

Activase 100 mg Reconstitution (use aseptic technique)

Step 1: Cleaning	
	<ul style="list-style-type: none"> • Remove caps from both vials. • Wipe both stoppers with alcohol swabs.
Step 2: Spiking Water Vial	
	<ul style="list-style-type: none"> • Remove cover from one end of transfer device (Note: Either side of transfer device can be used. Do not wipe transfer device spikes with alcohol.) • Insert spike straight through center of water vial stopper. <p>⚠ Do not invert water vial yet. Inverting too early may lead to leakage and incorrect dosing.</p>
Step 3: Spiking Activase Vial	
	<ul style="list-style-type: none"> • Remove cover from other end of transfer device. • Hold Activase vial upside down over spike. • Press Activase vial down to insert spike straight through center of Activase vial stopper. <p>⚠ Inserting the spike off-center could lead to stopper collapse.</p>

Step 4: Inverting and transferring	
	<ul style="list-style-type: none"> • Invert vials so that water vial is on top. • Allow all water to transfer into Activase vial. • If the flow does not start immediately or pauses, initiate the flow by flipping and re-inverting the vials. • Swirl gently and/or invert slowly to dissolve Activase powder. <p>⚠ Do not shake vials. Shaking may lead to excessive foaming and degraded medication.</p>
Step 5: Inspecting	
	<ul style="list-style-type: none"> • Separate empty water vial and transfer device from Activase vial. • Reconstituted Activase vial (1 mg/mL) should be: <ul style="list-style-type: none"> ○ Colorless to pale yellow and transparent ○ Free of particulates • If needed, let stand undisturbed for a few minutes to allow large bubbles to dissipate.

4.4 Administration

50 MG VIALS


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

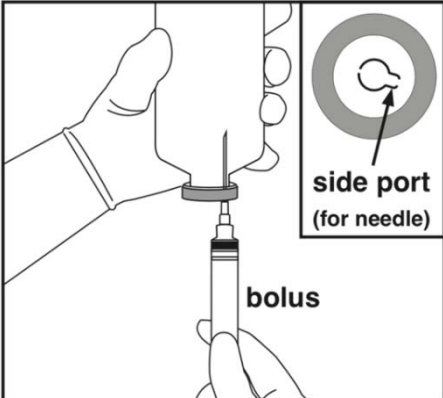
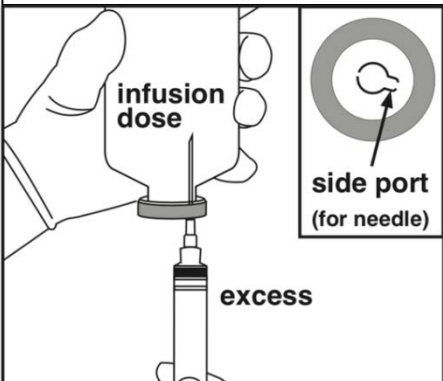
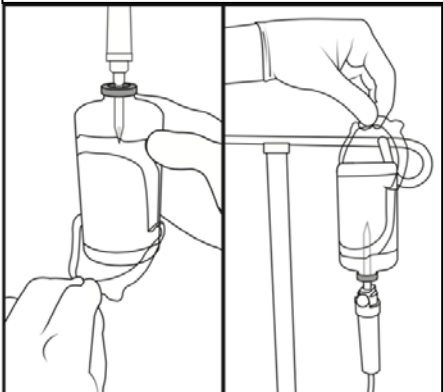
- By removing the appropriate volume from the vial of reconstituted (1-mg/mL) ACTIVASE rt-PA using a syringe and needle. The syringe should not be primed with air and the needle should be inserted into the ACTIVASE rt-PA vial stopper.
- By removing the appropriate volume from a port (second injection site) on the infusion line after the infusion set is primed.
- By programming an infusion pump to deliver the appropriate volume as a bolus at the initiation of the infusion.

The remainder of the ACTIVASE rt-PA dose may be administered using either a polyvinyl chloride bag or glass vial and infusion set.

100 MG VIALS

Activase 100 mg Administration (use aseptic technique)

Administration Warnings	
 <p>Review important information to the right before preparing dose.</p>	<p>⚠ Do not push air from the syringe into the vial.</p> <p>The vial is not under vacuum and adding air at any time may result in leakage and incorrect dosing.</p> <p>⚠ Only insert needles into the side port.</p> <p>Insert needle into side port of vial stopper when withdrawing medication to avoid leakage and incorrect dosing. Do not insert needles into center of stopper.</p>

Step 6: Preparing bolus	
	<ul style="list-style-type: none"> • Check if bolus is needed. If yes, attach needle to empty Luer syringe. • Insert needle through side port and withdraw bolus amount. <p>! Do not push any air from the syringe into vial (may cause leakage).</p> <ul style="list-style-type: none"> • Alternatively, the bolus can be left in the vial and administered via an infusion pump or removed from a port on the infusion line.
Step 7: Removing excess volume	
	<ul style="list-style-type: none"> • Check if there is excess volume in vial. If yes, attach needle to empty Luer syringe. • Insert needle through side port and withdraw excess volume. <p>! Do not push any air from syringe into vial (may cause leakage).</p> <ul style="list-style-type: none"> • Discard any excess volume. • Leave infusion dose in vial.
Step 8: Spiking and hanging	
	<ul style="list-style-type: none"> • Insert spike from IV tubing set into center of vial stopper, through same hole made by transfer device. <p>! Do not make a new hole in the vial stopper. Additional holes in vial stopper may lead to leakage.</p> <ul style="list-style-type: none"> • Peel clear plastic hanger from vial label. • Hang on IV pole and administer per facility protocol.

5 OVERDOSAGE

Overdosage could lead to serious bleeding. Should serious bleeding occur in a critical location, the infusion of ACTIVASE rt-PA (alteplase for injection) and any other concomitant anticoagulant should be discontinued immediately. If necessary, blood loss and reversal of the bleeding tendency can be managed with whole blood or packed red cells. In the event of clinically significant fibrinogen depletion, fresh frozen plasma or cryoprecipitate can be infused.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (I.V.)	Lyophilized powder for solution, 50 mg , 100 mg	L-arginine, phosphoric acid and polysorbate 80

Dosage Forms

ACTIVASE rt-PA (alteplase for injection) is supplied as a sterile, lyophilized powder in 50 mg vials with vacuum present and in 100 mg vials with no vacuum present.

Composition

The composition of the lyophilized product is alteplase (medicinal ingredient), L-arginine, phosphoric acid and polysorbate 80.

Packaging

ACTIVASE rt-PA is available in:

- Boxes each containing one (1) vial of ACTIVASE rt-PA 50 mg and one (1) vial of Sterile Water for Injection, USP 50 mL, for preparing a sterile solution of ACTIVASE rt-PA.
- Boxes each containing one (1) vial of ACTIVASE rt-PA 100 mg and one (1) vial of Sterile Water for Injection, USP 100 mL, and one transfer device for preparing a sterile solution of ACTIVASE rt-PA.

Description

ACTIVASE rt-PA (alteplase for injection) is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified fibrinolytic glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator. The manufacturing process involves the secretion of the serine protease alteplase into the culture medium by an established mammalian cell line into which the cDNA for tissue plasminogen activator has been genetically inserted.

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

The composition of the lyophilized product is alteplase (medicinal ingredient), L-arginine, phosphoric acid and polysorbate 80.

Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Biological potency is determined by an in vitro clot lysis assay and is expressed in International Units (58×10^4 I.U./mg ACTIVASE rt-PA).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

ACTIVASE rt-PA (alteplase for injection) must be administered in a hospital setting where the appropriate diagnostic and monitoring techniques are readily available.

Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE rt-PA and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

ACTIVASE rt-PA is a drug known to cause severe bleeding and an increased incidence of intracranial hemorrhage. Use of ACTIVASE rt-PA for the treatment of stroke is limited to physicians experienced in acute stroke management (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.).

A study of another alteplase product, Actilyse, in acute ischemic stroke, suggested that doses greater than 0.9 mg/kg may be associated with increased risk of ICH. **Doses greater than 0.9 mg/kg (maximum 90 mg) should not be used in the management of acute ischemic stroke.**

Based on burden of evidence, treatment of patients with acute ischemic stroke more than three hours after symptom onset is not recommended (see 2 CONTRAINDICATIONS). The risks of ACTIVASE rt-PA (alteplase for injection) 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 rt-PA treatment can be initiated prior to the availability of coagulation study results. However, infusion should be discontinued if either a pre-treatment International Normalized Ratio (INR) > 1.7 or a prothrombin time (PT) >15 seconds or an elevated activated partial thromboplastin time (aPTT) is identified.

Treatment must be limited to facilities that can provide appropriate evaluation and management of ICH.

Cardiovascular

Thromboembolism

- The use of thrombolytics including ACTIVASE can increase the risk of thrombo-embolic events in patients with left heart thrombus, e.g., mitral stenosis or atrial fibrillation.

Cholesterol Embolization

- Cholesterol embolization 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 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.

Hematologic

The most common complication encountered during therapy with ACTIVASE rt-PA (alteplase for injection) is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding involving the gastrointestinal tract, genitourinary tract, respiratory tract, retroperitoneal or intracranial sites
- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g. venous cutdowns, arterial punctures, sites of recent surgical intervention)

Fibrin will be lysed during the infusion of ACTIVASE rt-PA and bleeding from recent puncture sites may occur. Therefore, therapy with ACTIVASE rt-PA, as with other thrombolytic agents, requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

Rare fatal cases of hemorrhage associated with traumatic intubation in patients administered ACTIVASE rt-PA have been reported.

Intramuscular injections and nonessential handling of the patient should be avoided during and immediately following treatment with ACTIVASE rt-PA. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE rt-PA, 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 in a critical location (not controllable by local pressure) occur, the infusion of ACTIVASE rt-PA and any other concomitant anticoagulant should be discontinued immediately and treatment initiated (See 5 OVERDOSAGE).

In the following conditions, the risks of ACTIVASE rt-PA therapy may be increased and should be weighed against the anticipated benefits:

- Recent (within 10 days) major surgery, e.g. coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels
- Clinical evidence or history of transient ischemic attacks
- Recent gastrointestinal or genitourinary bleeding (within 10 days)
- Recent trauma (within 10 days)
- Hypertension: systolic BP \geq 175 mm Hg and/or diastolic BP \geq 110 mm Hg
- A history or clinical evidence of hypertensive disease in a patient over 70 years old

- Advanced age, e.g. over 75 years old
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Significant liver dysfunction, e.g. prolonged prothrombin time
- Pregnancy
- Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- 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

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.

Immune

Angioedema has been observed in post-market experience in patients treated for acute ischemic stroke (see 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS). Onset of angioedema occurred during and up to 2 hours after infusion of ACTIVASE rt-PA. In many cases, patients were receiving concomitant Angiotensin-converting enzyme inhibitors. Patients treated with ACTIVASE rt-PA should be monitored during and for several hours after infusion for signs of hypersensitivity. If signs of hypersensitivity occur, e.g. anaphylactoid reaction or angioedema develops, promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids or epinephrine) and discontinue the ACTIVASE rt-PA infusion.

Monitoring and Laboratory Tests

During ACTIVASE rt-PA infusion, coagulation tests and/or measures of fibrinolytic activity may be performed if desired. However, routine measurements of fibrinogen as well as fibrinogen degradation products are unreliable, and should not be undertaken unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE rt-PA is a serine protease that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in a blood sample removed for analysis. Collection of blood samples on aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Sensitivity/Resistance

Anaphylactoid reactions associated with the administration of ACTIVASE rt-PA are rare and can be caused by hypersensitivity to the active substance alteplase or to any of the excipients. Rare fatal outcome for hypersensitivity was reported.

There has been little documentation of readministration of ACTIVASE rt-PA. Readministration should be undertaken with caution. Less than 0.5% of patients receiving single courses of ACTIVASE rt-PA therapy have experienced transient antibody formation. Nevertheless, if an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

7.1 Special Populations

7.1.1 Pregnant Women

ACTIVASE rt-PA 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 rt-PA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breast-feeding

It is not known whether ACTIVASE rt-PA is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness of ACTIVASE rt-PA in children (age less than 18 years) has not been established. Therefore, treatment of such patients is not recommended.

7.1.4 Geriatrics

Geriatrics (>77 years of age): Evidence from clinical studies and experience suggests that risks of therapy may be increased in the elderly. In ACTIVASE rt-PA treated patients (NINDS study) of advanced age (e.g. >77 years of age), the trend toward increased risk for symptomatic ICH within the first 36 hours was more prominent. Similar trends were also seen for total ICH and for all-cause 90-day mortality. Analyses for efficacy suggested a reduced but still favourable clinical outcome for these patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Bleeding: General

The most frequent adverse reaction associated with ACTIVASE rt-PA (alteplase for injection) is bleeding. Sometimes fatal outcome has been reported in patients who have experienced serious bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving the gastrointestinal tract, genitourinary tract, respiratory tract, retroperitoneal or intracranial sites
- Superficial or surface bleeding due to lysis of fibrin in the hemostatic plug. Therefore, ACTIVASE rt-PA therapy requires careful attention to potential bleeding sites such as venous cutdowns, catheter insertion sites, arterial puncture sites, and any site of recent surgical intervention.

Bleeding events other than ICH were noted in the studies of acute ischemic stroke and were consistent with the general safety profile of ACTIVASE rt-PA. 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 rt-PA treated patients compared to 3.8% for placebo (p = 0.19, using Mantel-Haenszel Chi-Square).

HYPERSENSITIVITY

Hypersensitivity reactions, e.g. anaphylactoid reaction, anaphylactic reaction, laryngeal edema, rash, urticaria angioedema and shock (see WARNINGS AND PRECAUTIONS) have been reported. A cause and effect relationship has not been established. When such reactions occur they usually respond to conventional therapy. A rare fatal outcome for hypersensitivity has been reported.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The incidence of ICH, especially symptomatic ICH, in patients with acute ischemic stroke was higher in ACTIVASE rt-PA treated patients than placebo patients (see also 10 CLINICAL PHARMACOLOGY section).

The incidences of ICH, and new ischemic stroke following ACTIVASE rt-PA treatment compared to placebo are presented in Table 1 as a combined safety analysis (n = 624) for Parts 1 and 2. These data indicated a significant increase in ICH following ACTIVASE t rt-PA treatment, particularly symptomatic ICH within 36 hours. Symptomatic ICH within 36 hours was experienced by 2 of 312 (0.6%) of placebo-treated patients and 20 of 312 (6.4%) ACTIVASE rt-PA treated patients (p<0.01). Potential predictors of symptomatic ICH within 36 hours of study drug administration were baseline values of NIHSS score, fibrinogen (<200mg/dL), and platelet count (<150,000/uL). These predictors were the same in both treatment groups.

Table 1 The NINDS t-PA Stroke Trial Safety Outcome

	Part 1 and Part 2 Combined		
	Placebo (n = 312)	ACTIVASE rt-PA (n = 312)	p-Value ²
Total ICH ¹	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

¹Within 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.

²Fisher's Exact Test

Table 2 displays the incidences of all-cause 90-day mortality and mortality rates and odds ratios by baseline NIHSS subgroup. In ACTIVASE rt-PA treated patients, there were no increases compared to placebo in the incidences of 90-day mortality or severe disability but all-cause 90-day mortality rates increased in both treatment groups with higher baseline NIHSS score category. As with any subgroup analysis, these results should be viewed with caution. However, there appeared to be a (non-significant) trend toward higher mortality for ACTIVASE rt-PA patients with baseline NIHSS scores > 20. Only 22% of the NINDS study patients were in this subgroup, and the observed proportions are therefore based on small denominators. Whilst the interpretation of any subgroup should be undertaken with caution, these figures are included to assist physicians in the assessment of the risk-benefit ratio for a particular patient.

Table 2 All-cause 90-Day Mortality for Baseline NIHSS Subgroups

Baseline NIHSS Score	Placebo (n=312)	ACTIVASE rt-PA (n=312)	Odds Ratio and 95% CI
All-cause 90 day mortality	64 (20.5%) 9/99 (9.1%)	54 (17.3%) 2/110 (1.8%)	p-Value 0.36 5.40 (1.14, 25.63) ^a
0-10	26/136 (19.1%)	22/139 (15.8%)	1.26 (0.67, 2.35)
11-20	29/77 (37.7%)	30/63 (47.6%)	0.67 (0.34, 1.31)
>20			

Odds ratios > 1 indicate benefit for ACTIVASE rt-PA patients. (Where 95% CIs include 1, difference is non-significant on this sample size).

^a Significant difference (p<0.05).

8.3 Less Common Clinical Trial Adverse Reactions

Not Applicable.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Not Applicable.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported among patients receiving ACTIVASE rt-PA in clinical trials and in post marketing experience. These reactions are frequent sequelae of the underlying disease and the effect of ACTIVASE rt-PA on the incidence of these events is unknown.

Use in Acute Ischemic Stroke: cerebral edema, cerebral herniation, seizure, new ischemic stroke, embolism. These events may be life threatening and may lead to death.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Not Applicable.

9.2 Drug Interactions Overview

Not Applicable.

9.3 Drug-Behavioural Interactions

Not Applicable.

9.4 Drug-Drug Interactions

The interaction of ACTIVASE rt-PA with other drugs has not been studied. In addition to bleeding associated with anticoagulants such as heparin and warfarin, drugs that alter platelet function (such as acetylsalicylic acid) may increase the risk of bleeding if administered prior to, during or after ACTIVASE rt-PA infusion.

Angioedema has been observed after ACTIVASE rt-PA administration in patients receiving concomitant ACE inhibitor therapy. However, the significance of this observation has not been determined (see 8 ADVERSE REACTIONS).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ACTIVASE rt-PA (alteplase for injection) is a serine protease which has the property of fibrin-enhanced conversion of plasminogen to plasmin. ACTIVASE rt-PA produces minimal conversion of plasminogen in the absence of fibrin; and when introduced into the systemic circulation, ACTIVASE rt-PA binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with minimal systemic effects. Following administration of ACTIVASE rt-PA, there is a decrease (20-30%) in circulating fibrinogen. Decreases in plasminogen and α 2-antiplasmin are also evident.

10.2 Pharmacodynamics

Not Applicable.

10.3 Pharmacokinetics

Elimination

ACTIVASE rt-PA is cleared rapidly from circulating plasma with an initial half-life of less than 5 minutes. The plasma clearance of ACTIVASE rt-PA is approximately 500 mL/min. The clearance is mediated primarily by the liver.

11 STORAGE, STABILITY AND DISPOSAL

Lyophilized ACTIVASE rt-PA is stable up to the expiration date stamped on the vial when stored at controlled temperatures between 2°C and 30°C. Protect the lyophilized material during extended storage from excessive exposure to light.

Unused reconstituted ACTIVASE rt-PA (in the vial) may be stored at 2-30°C for up to 8 hours. After that time, any unused portion of the reconstituted material should be discarded. During the period of reconstitution and infusion, protection from light is not necessary.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ACTIVASE® rt-PA

Chemical name: alteplase for injection

Molecular formula, Structural formula and molecular mass:

Figure 1: The linear sequence of rt- PA. Amino acid residues are identified by the single letter code. Disulfide bonds are denoted by solid lines connecting cysteine residues.

There are 17 disulfide bonds in rt-PA found between cysteine residues (see Figure 1).

FIGURE 1

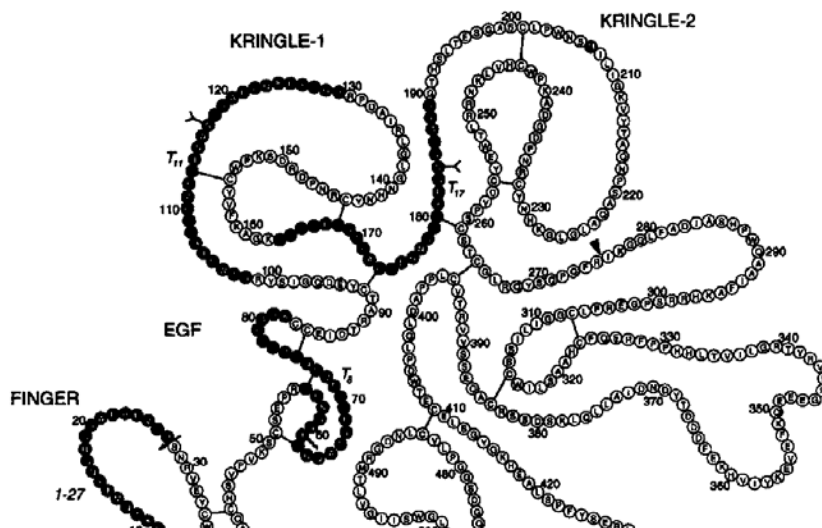


FIGURE 2

rt-PA (527 res.)

SYQVICRDEKTQMIYQQHQSWLRPVLRSNRVEYCWNSGRAQCHSVPVKSCSEPRCFNG
GTCQQALYFSDFVCQCPEGFAGKCCEIDTRATCYEDQGISYRGTWSTAESGAECTNWNSS
ALAQKPYSGRRPDAIRLGLGNHNYCRNPDRDSKPWCYVFKAGKYSSEFCSTPACSEGNSDC
YFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSAQUALGLGKHNYCRNPDGDAK
PWCHVLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSP
GERFLCGGILISSCWILSAAHCFQERFPPHHLTVILGRTYRVVPGEEEQKFEVEKYIVHKEFDD
DTYDNDIALQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERL
KEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVCLND
GRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNMRP

The purified glycoprotein contains 527 amino acids with an approximate molecular weight of 65,000 daltons.

The relative molecular mass is between 55 and 66 kD as measured by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Activase[®] is expressed as a 59kD protein. The addition of carbohydrate moieties brings the apparent molecular weight as determined by SDS PAGE to closer to 65 kD.

Physicochemical properties:

The isoelectric focusing (IEF) pattern of rt-PA has multiple bands between pH 5.8 and 8.4. The isoelectric point (pI) for rt-PA exhibits heterogeneity due to deamidation, proteolysis, and sialic acid.

Product Characteristics:

ACTIVASE rt-PA (alteplase for injection) is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified fibrinolytic glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator. The manufacturing process involves the secretion of the serine protease alteplase into the culture medium by an established mammalian cell line into which the cDNA for tissue plasminogen activator has been genetically inserted.

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

The composition of the lyophilized product is alteplase (medicinal ingredient), L-arginine, phosphoric acid and polysorbate 80.

Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Biological potency is determined by an in vitro clot lysis assay and is expressed in International Units (58×10^4 I.U./mg ACTIVASE rt-PA).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

NINDS Study Summary

The National Institute of Neurological Disorders and Stroke (NINDS) acute ischemic stroke study³¹ randomized 624 patients to a double-blind, placebo controlled trial using i.v. t-PA in a dose of 0.9 mg/kg t-PA to a maximum of 90 mg, with 10% of the total dose given as a bolus over 1-2 minutes and the remainder of the dose infused over 60 minutes. Patients were treated within 3 hours of a well-defined symptom onset after exclusion of the presence of intracranial hemorrhage (ICH) by cranial computerized tomography (CT) scan. Additional exclusion criteria were included in the protocol (see CONTRAINDICATIONS).

Efficacy outcomes at 3 months as measured by the outcome scales follow (Table 4).

CASES Study Summary

The Canadian ACTIVASE rt-PA for Stroke Effectiveness Study (CASES) was a post-marketing clinical programme conducted in collaboration with the Canadian Stroke Consortium, the Heart & Stroke Foundation of Canada, the Canadian Stroke Society, and the Canadian Stroke Network. CASES investigators enrolled 1135 patients treated with i.v. ACTIVASE rt-PA in a prospective, uncontrolled, multi-centre, observational study designed to assess safety and effectiveness and compare these outcomes to previously reported randomized trial data. A total of 60 centres participated: 27 (45%) academic/tertiary care hospitals and 33 (55%) community hospitals. 10 centres (all were academic/tertiary care hospitals) were high volume hospitals (1 or more patients per month) enrolling 61% of patients. No differences in the rate of good outcome or symptomatic ICH were observed

between high-volume and low-volume centres or between academic/tertiary care hospitals and community hospitals. Multivariable adjustment did not modify this observation. Patients were elderly (median age 73, mean 70) and were approximately evenly distributed between males (53.5%) and females (46.5%). The severity of stroke was significant (median NIHSS=14) and similar to that observed in the NINDS study.

The incidence of symptomatic ICH was 4.6% which is comparable to the 6.4% rate seen in the NINDS study. Among patients who suffered symptomatic ICH, 39/52 (75%) were fatal in hospital. The 3 month outcomes were comparable to the results of the NINDS study with 30% of patients achieving a normal or near-normal neurological examination (NIHSS score 0-1) and 38% achieving either no functional disability or return to the previous level of functioning using the Modified Rankin Scale.

14.2 Study Results

Table 4 The NINDS t-PA Stroke Trial, Part 2 - 3-Month Efficacy Outcomes

□	□ FREQUENCY OF FAVOURABLE OUTCOME ¹		
	Placebo (n=165)	ACTIVASE rt-PA (n=168)	Absolute Difference (95% CI)
Analysis			
Barthel Index	37.6%	50.0%	12.4% (3.0, 21.9)
Modified Rankin Scale	26.1%	38.7%	12.6% (3.7, 21.6)
Glasgow Outcome Scale	31.5%	44.0%	12.5% (3.3, 21.8)
NIHSS	20.0%	31.0%	11.0% (2.6, 19.3)

¹Favourable Outcome is defined as recovery with minimal or no disability.

The NINDS protocol required close patient monitoring and blood pressure management to maintain systolic blood pressure below 185 mm Hg and diastolic pressure less than 110 mm Hg for 24 hours. Blood pressure was monitored during the hospital stay. Intravenous labetalol using 10 mg boluses over 1-2 minutes repeated every 10-20 minutes has been recommended as part of the NINDS protocol for blood pressures above these limits to reduce the risk of intracranial hemorrhage.

The risks of ACTIVASE rt-PA therapy must be weighed against potential benefits in patients in the following circumstances:

1. Patients with severe neurological deficits at presentation (e.g. NIH Stroke Scale > 22). There is an increased risk of intracerebral hemorrhage in these patients (odds ratio 1.8; 95% CI, 1.2-1.9)

2. Patients with substantial brain edema (acute hypodensity) or mass effect on CT before treatment. Major CT changes of an early infarct are associated with increased risk of intracerebral bleeding.

Additional information on the NINDS study is presented under the CLINICAL PHARMACOLOGY section of this monograph.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The safety of the pharmacological administration of rt-PA was evaluated by conducting acute and subacute toxicity studies in rats, dogs and monkeys.

Acute Toxicology

1. Rats were monitored for fourteen days after receiving one intravenous bolus injection of rt-PA at dosages of 0.5, 1.5 and 5.0 mg/kg. Additional acute toxicity studies were conducted in rats and these studies employed rt-PA at dosages of 1, 3 and 10 mg/kg given as an intravenous bolus injection. In all studies there were no deaths during the study period, no significant toxic signs observed, and no rt-PA related macroscopic changes observed at the terminal necropsy.
2. Cynomolgus monkeys were administered rt-PA at doses of 1, 3 and 10 mg/kg infused intravenously for 60 minutes. All of the animals appeared normal for the entire observation period of 7 days.

There were no significant effects of rt-PA on the electrocardiograms, heart rate, systolic blood pressure or hematological parameters. Consistent with its pharmacologic activity, rt-PA caused significant fibrinogenolysis at the doses of 3 and 10 mg/kg. Fibrinogen levels at 2 and 4 hours after rt-PA infusion were decreased to about 60% of excipient controls with the 3 mg/kg dose and about 18% of controls with the 10 mg/kg dose. Fibrin/fibrinogen degradation products were increased at 2 and 4 hours after rt-PA infusion. The parameters were not significantly different from excipient controls at 24 hours. rt-PA did not induce any unexpected physiological or pathological changes in the Cynomolgus monkeys.

Sub-acute Toxicology

1. In rats, dosages of 1, 3 and 10 mg/kg were given daily for 14 days via the tail vein. All results were considered to be comparable and normal between treated animals and those in the excipient control group, except for small changes in the hematology determinations including significantly lower mean erythrocyte, hemoglobin and haematocrit values as compared to control values. These changes were consistent with a mild anaemia and occurred primarily in females at 3 and 10 mg/kg/day.
2. Dogs were given doses of 0.5, 1.0 and 1.5 mg/kg/day (6-hour intravenous infusion) for 14 days. There was no evidence of any systemic toxicity related to the test article at any dosage level, or in any dog in the excipient control group.
3. Beagle dogs were given rt-PA as a six hour i.v. infusion at 1, 2, 3 and 10 mg/kg/day for 14 days. There were some hematological changes observed which were consistent with mild anaemia (e.g.

decreased hemoglobin, hematocrit and erythrocytes) in the 3 and 10 mg/kg/day groups. Serum biochemical and urine analyses were comparable to control values. There was little or no change in the levels of fibrinogen and fibrinogen degradation products in plasma samples taken approximately 18 hours after the infusion was completed. Electrocardiograms were normal in all dose groups. Gross and microscopic pathology revealed evidence of hemorrhage and fibrosis at the injection site; this occurred in all dose groups including some dogs in the control group.

In addition, evidence of hemorrhage was observed at sites distant to the injection site, including various locations in the gastrointestinal tract, in 4 of 6 dogs which received 10 mg/kg/day. Organ weights were comparable between treated and control animals.

Summary of Acute and Sub-acute Toxicology

Acute and sub-acute toxicity studies in the rat, dog and monkey demonstrated no acute systemic toxicity. In subacute studies, significant systemic toxicity was observed only in dogs given doses of 10 mg/kg/day for 14 days and consisted of hemorrhagic sites, primarily in the gastrointestinal tract. A mild anaemia was observed in rats and dogs at dosages of 3 and 10 mg/kg/day for 14 days; this could be due to the hemorrhage which was detected at the injection site.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ACTIVASE RT-PA

alteplase for injection

Read this carefully before you start taking **ACTIVASE RT-PA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ACTIVASE RT-PA**.

Serious Warnings and Precautions

- ACTIVASE rt-PA is a drug known to cause severe bleeding and an increased incidence of bleeding in the skull.
- Use of ACTIVASE rt-PA for the treatment of stroke is limited to physicians experienced in acute stroke management, who are treating patients in a hospital setting.

What is ACTIVASE RT-PA used for?

- ACTIVASE rt-PA is indicated for the management of acute ischemic stroke (AIS) in adults for improving neurological recovery and reducing the incidence of disability

How does ACTIVASE RT-PA work?

- ACTIVASE rt-PA, when introduced into the blood circulation, will bind to fibrin (protein that prevents the flow of blood) in blood clots and converts the entrapped plasminogen to plasmin (which breaks down fibrin clots).

What are the ingredients in ACTIVASE RT-PA?

Medicinal ingredients: alteplase

Important Non-medicinal ingredients: L-arginine, phosphoric acid and polysorbate 80

ACTIVASE RT-PA comes in the following dosage forms:

- Boxes each containing one (1) vial of ACTIVASE rt-PA 50 mg and one (1) vial of Sterile Water for Injection, USP 50 mL, for preparing a sterile solution of ACTIVASE rt-PA.
- Boxes each containing one (1) vial of ACTIVASE rt-PA 100 mg and one (1) vial of Sterile Water for Injection, USP 100 mL, and one transfer device for preparing a sterile solution of ACTIVASE rt-PA

Do not use ACTIVASE RT-PA if you have:

- Hypersensitivity to alteplase or to any ingredient in the formulation or components of the container
- Symptom onset greater than 3 hours
- Bleeding disorder or recent history of bleeding
- Recent major surgery or trauma
- Uncontrolled high blood pressure (e.g., > 185 mm Hg systolic or >110 mm Hg diastolic)

- Treatment required to reduce blood pressure
- Seizure at the onset of stroke
- Brain tumour, abnormality of the blood vessels, or aneurysm
- Recent gastrointestinal or urinary tract bleeding
- Recent arterial puncture
- Abnormal blood glucose levels
- Recent heart attack or heart lining inflammation

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ACTIVASE RT-PA. Talk about any health conditions or problems you may have, including if you have:

- Severe problems with the nerve, spinal cord or brain function
- Major early infarct signs such as swelling, growing mass, or midline shift (detected through a CT scan)
- Recent major surgery or trauma
- Clinical evidence or history of transient ischemic attacks
- Recent gastrointestinal or urinary tract bleeding
- High blood pressure (i.e., ≥ 175 mm Hg systolic and/or ≥ 110 mm Hg diastolic)
- History or clinical evidence of high blood pressure in a patient over 70 years old
- Over 75 years old
- Problems with the heart or heartbeat
- Severe liver failure
- Pregnancy
- Serious infection or inflammation
- Taking medications that affect blood clotting (i.e., warfarin sodium)
- Use of blood dissolving drugs
- Cholesterol embolization
- Abnormal blood glucose levels

Other warnings you should know about:

- **Treatment of patients with problems with nerve, spinal cord or brain function or with rapidly improving symptoms is not recommended.**
- The most common complication encountered during therapy with ACTIVASE rt-PA (alteplase for injection) is bleeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ACTIVASE RT-PA:

- Anticoagulants such as heparin and warfarin
- Drugs that alter platelet function (such as acetylsalicylic acid)
- Angiotensin-converting enzyme (ACE) inhibitors

How to take ACTIVASE RT-PA:

- ACTIVASE rt-PA (alteplase for injection) is intended for intravenous use only.

Usual dose:

The recommended dose is 0.9 mg/kg (maximum of 90 mg) infused over 60-minutes with 10% of the total dose administered as an initial intravenous bolus over 1 minute. The recommended total dose is based upon patient weight.

Refer to Product Monograph Part I – Health Professional Information – DOSAGE AND ADMINISTRATION section for additional Preparation and Administration information.

Overdose:

Overdosage could lead to serious bleeding.

Should serious bleeding occur in a critical location, the infusion of ACTIVASE rt-PA (alteplase for injection) and any other concomitant anticoagulant should be discontinued immediately. If necessary, blood loss and reversal of the bleeding tendency can be managed with whole blood or packed red cells.

In the event of clinically significant fibrinogen depletion, you may be infused with fresh frozen plasma or cryoprecipitate.

If you think you, or a person you are caring for, have taken too much ACTIVASE RT-PA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using ACTIVASE RT-PA?

Like all medicines, ACTIVASE rt-PA can have side effects. Below are some of the side effects associated with ACTIVASE rt-PA:

- Allergic-type reactions, e.g. anaphylactoid reaction, anaphylactic reaction, throat swelling, angioedema, rash, hives, shock
- Potential bleeding sites as a result of recent invasive procedure (i.e., catheter insertions, puncture, surgery)

For any unexpected effects while taking ACTIVASE rt-PA, contact your doctor or pharmacist.

In all cases, the health care professional will decide whether the drug should be stopped or not.

These are not all the possible side effects you may have when taking ACTIVASE RT-PA. If you experience any side effects not listed here, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Swelling or high pressure in the brain, uncontrollable shaking		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
(seizure), new ischemic stroke, embolism			
Internal bleeding, involving the gastrointestinal and urinary tract, lungs, or within the skull		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2°C and 30°C. Protect from excessive exposure to light.

Unused reconstituted ACTIVASE rt-PA (in the vial) may be stored at 2-30°C for up to 8 hours. After that time, any unused portion of the reconstituted material should be discarded.

During the period of reconstitution and infusion, protection from light is not necessary.

Keep out of reach and sight of children.

If you want more information about ACTIVASE RT-PA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.rochecanada.com> or by contacting the sponsor Hoffmann-La Roche Limited, at: 1-888-762-4388)

This leaflet was prepared by Hoffmann-La Roche Limited

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Last Revised: October 7, 2021

Activase®
(alteplase)
for infusion
100 mg (58 million IU)



Read before preparing Activase®

Instructions for Use

See package insert for full prescribing information

Activase® (alteplase)

Kit Contents

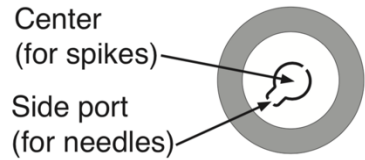
Transfer device



Activase vial
(no vacuum)



Activase vial stopper parts:



Sterile Water for Injection (water) vial

Note:

Do not use Bacteriostatic Water for Injection, USP.



Prescribing Information

Instructions for Use

Activase® (alteplase)

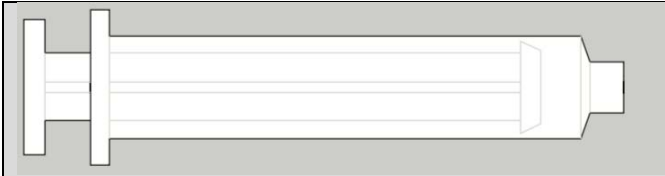
Also Required

(not included in kit)

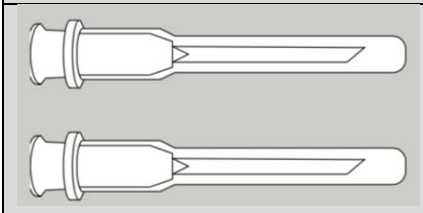
1 Luer Syringe for removing bolus dose, as needed



1 Luer syringe for removing excess volume, as needed



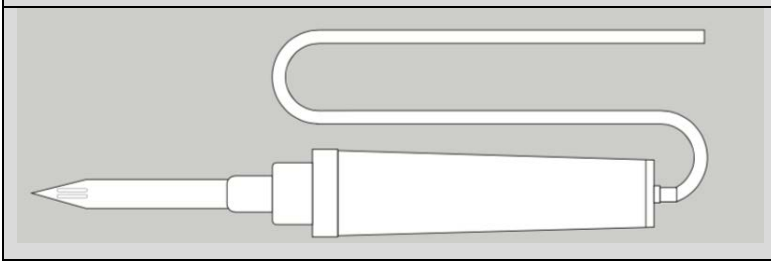
2 large bore needles

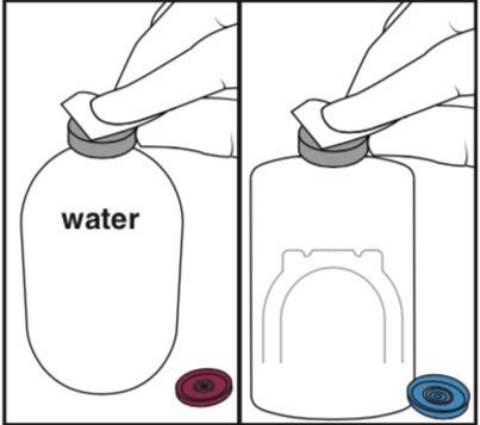
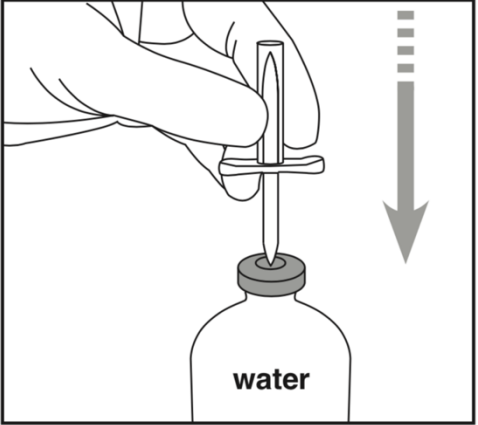
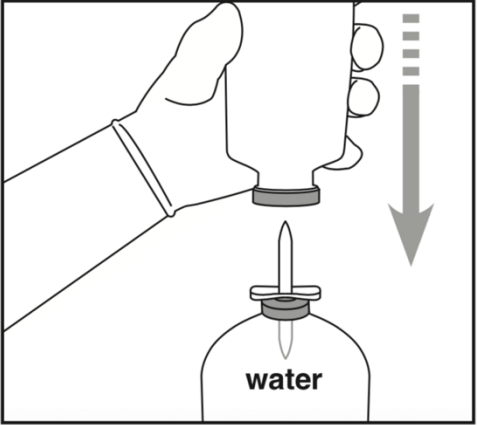


2 Alcohol swabs

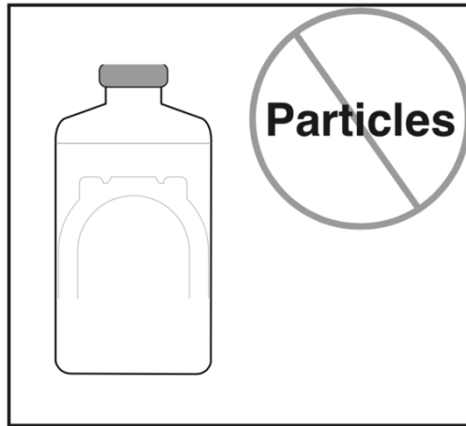
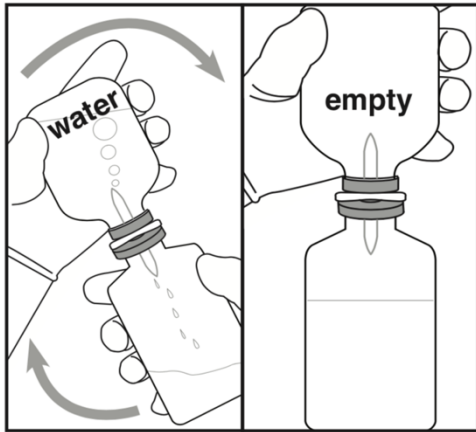


IV infusion set



Activase® (alteplase)	Activase® (alteplase)	Activase® (alteplase)
Reconstitution (use aseptic technique)		
Step 1: Cleaning	Step 2: Spiking Water vial	Step 3: Spiking Activase vial
		
<ul style="list-style-type: none"> ● Remove caps from both vials. ● Wipe both stoppers with alcohol swabs. 	<ul style="list-style-type: none"> ● Remove cover from one end of transfer device (Note: Either side of transfer device can be used. Do not wipe transfer device spikes with alcohol). ● Insert spike straight through center of water vial stopper. <p>⚠ Do not invert water vial yet. Inverting too early may lead to leakage and incorrect dosing.</p>	<ul style="list-style-type: none"> ● Remove cover from other end of transfer device. ● Hold Activase vial upside down over spike. ● Press Activase vial down to insert spike straight through center of Activase vial stopper. <p>⚠ Inserting the spike off-center could lead to stopper collapse.</p>

Activase® (alteplase)	Activase® (alteplase)	Activase® (alteplase)
Reconstitution (use aseptic technique)		Administration Warning
Step 4: Inverting and transferring	Step 5: Inspecting	



- Invert vials so that water vial is on top.
- Allow all water to transfer into Activase vial.
- If the flow does not start immediately or pauses, initiate the flow by flipping and re-inverting the vials.
- Swirl gently and/or invert slowly to dissolve Activase powder.

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

- Separate empty water vial and transfer device from Activase vial.
- Activase should be free of:
 - Discoloration
 - Particulates
- If needed, let stand undisturbed for a few minutes to allow large bubbles to dissipate.

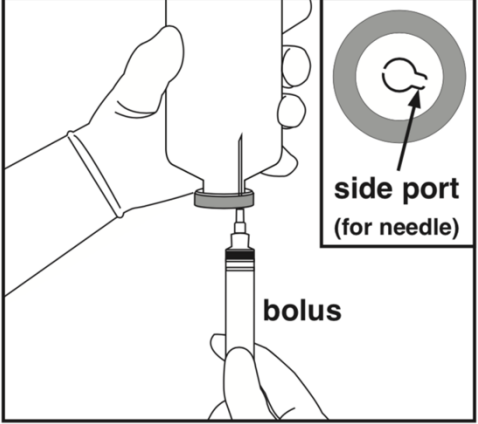
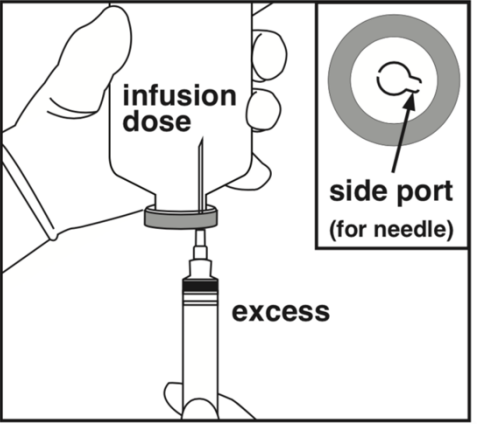
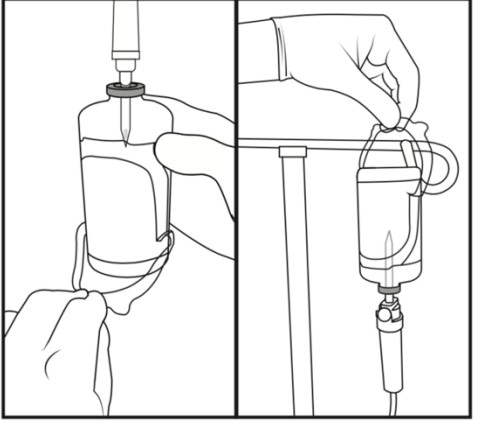
Review important information below before preparing dose.

! 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 into the side port.

Insert needle into side port of vial stopper when withdrawing medication to avoid leakage and incorrect dosing. Do not insert needles into center of stopper.

Activase® (alteplase)	Activase® (alteplase)	Activase® (alteplase)
Administration (use aseptic technique)		
Step 6: Preparing bolus	Step 7: Removing excess volume	Step 8: Spiking and hanging
		

<ul style="list-style-type: none"> • Check if bolus is needed. If yes, attach needle to empty Luer syringe. • Insert needle through side port and withdraw bolus amount. <p>⚠ Do not push any air from syringe into vial (may cause leakage).</p> <ul style="list-style-type: none"> • Alternatively, the bolus can be left in the vial and administered via an infusion pump or removed from a port on the infusion line. 	<ul style="list-style-type: none"> • Check if there is excess volume in vial. If yes, attach needle to empty Luer syringe. • Insert needle through side port and withdraw excess volume. <p>⚠ Do not push any air from syringe into vial (may cause leakage).</p> <ul style="list-style-type: none"> • Discard any excess volume. • Leave infusion dose in vial. 	<ul style="list-style-type: none"> • Insert spike from IV tubing set into center of vial stopper, through same hole made by transfer device. <p>⚠ Do not make a new hole in the vial stopper. Additional holes in vial stopper may lead to leakage.</p> <ul style="list-style-type: none"> • Peel clear plastic hanger from vial label. • Hang on IV pole and administer per facility protocol.
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<p>Administration Notes</p>
<ul style="list-style-type: none"> • 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 that IV site and apply local therapy. • See full prescribing information for alternative dilution instructions.
<p>Storage & Stability</p>
<ul style="list-style-type: none"> • Protect the lyophilized Activase vial from excessive exposure to light. • Activase contains no antibacterial preservatives and must be used within 8 hours following reconstitution (when stored 2–30°C).