PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrACTIVASE® rt-PA

alteplase for injection

Lyophilized powder for injection - 50 mg and 100 mg

Fibrinolytic Agent

ACUTE MYOCARDIAL INFARCTION INDICATION ONLY

Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario
L5N 5M8

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DEC 31, 1996

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www.rochecanada.com

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.3 Reconstitution	04/2024
4 Dosage and Administration, 4.4 Administration	04/2024

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

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACTIVASE rt-PA (alteplase for injection) is indicated for intravenous use in adults for:

1) the lysis of suspected occlusive coronary artery thrombi associated with evolving transmural myocardial infarction; and

2) the reduction of mortality associated with acute myocardial infarction (AMI), the improvement of ventricular function following AMI and the reduction in the incidence of congestive heart failure.

Treatment should be initiated as soon as possible after the onset of acute myocardial symptoms. Greater benefit appears to be associated with earlier treatment of ACTIVASE rt-PA, following the onset of symptoms.

ACTIVASE rt-PA is effective in patients in whom therapy is initiated within six (6) hours of onset of symptoms for the accelerated infusion regimen or up to twelve (12) hours after onset of symptoms for the 3-hour infusion regimen. The GUSTO study was designed to enrol patients within a 6-hour period following the onset of myocardial infarct symptoms. The data available from this trial are insufficient to support a recommendation for use of the accelerated infusion regimen in patients presenting more than six (6) hours after the onset of symptoms.

For information on use in acute ischemic stroke (AIS), please consult the product monograph for the AIS indication.

1.1 Pediatrics

- Safety and effectiveness of ACTIVASE rt-PA in children has not been established. Therefore, treatment of such patients is not recommended.

1.2 Geriatrics

- The risks of therapy may be increased in the elderly (see ADVERSE REACTIONS, ACTIONS AND CLINICAL PHARMACOLOGY).

2 CONTRAINDICATIONS

ACTIVASE rt-PA (alteplase for injection) should not be administered to patients with known hypersensitivity to the active substance alteplase or to any ingredient in the formulation or components of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

ACTIVASE rt-PA (alteplase for injection) therapy is contraindicated in the following situations because of an increased risk of bleeding:

- Active internal bleeding

- History of stroke
- Patients receiving other intravenous thrombolytic agents
- Recent (within two months) intracranial, or intraspinal surgery or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled hypertension (systolic BP $\geq$ 180 mm Hg and/or diastolic BP $\geq$ 110 mm Hg)
- Recent traumatic cardiopulmonary resuscitation
- Recent severe trauma

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.

Administer ACTIVASE rt-PA as soon as possible after the onset of symptoms.

Anticoagulation During and After Treatment with ACTIVASE rt-PA

To date, heparin has been administered concomitantly in more than 90% of patients given ACTIVASE rt-PA. Adjunctive intravenous heparin administration is recommended to obtain a therapeutic partial thromboplastin time (PTT). The infusion of heparin should be initiated prior to the termination of the infusion of ACTIVASE rt-PA.

4.2 Recommended Dose and Dosage Adjustment

There are two dose regimens for ACTIVASE rt-PA for use in the management of AMI. The comparative efficacy of these two regimens has not been evaluated.

90-MINUTE ACCELERATED INFUSION

The recommended total dose is based upon patient weight, not to exceed 100 mg. For patients weighing >67 kg, the recommended dose is 100 mg, administered as a 15 mg intravenous bolus, followed by 50 mg infused over 30 minutes and then 35 mg infused over the next 60 minutes.

For patients weighing < 67 kg, the recommended dose is 15 mg administered as an intravenous bolus, followed by 0.75 mg/kg to a maximum of 50 mg, infused over the next 30 minutes, and then 0.50 mg/kg to a maximum of 35 mg infused over the next 60 minutes.

This 90-minute infusion regimen is recommended for use up to 6 hours after onset of AMI symptoms.

Accelerated Regimen: Infusion Chart

Patient Weight		Bolus	Volume of tPA added to empty pvc bag or glass vial (mL)	0.75 mg/kg over 30 Minutes			0.50 mg/kg over 60 Minutes			tPA Total Dose (mg) (Bolus + Maintenance) (Maximum Dose = 100 mg)
(lb)	(kg)	15 mg (15 mL) over 2 minutes		Infusion Dose (mg) (Max Dose = 50 mg)	Infusion Rate (mL/hr)	Volume to be Infused (mL)	Infusion Dose (mg) (Max Dose = 35 mg)	Infusion Rate (mL/hr)	Volume to be Infused (mL)	
90-94	41-42	15 mL	52 mL	31	62	31 mL	21	21	21mL	67
95-97	43-44	15 mL	54 mL	32	64	32 mL	22	22	22mL	69
98-104	45-47	15 mL	57 mL	34	68	34 mL	23	23	23mL	72
105-109	48-49	15 mL	60 mL	36	72	36 mL	24	24	24mL	75
110-114	50-51	15 mL	63 mL	38	75	38 mL	25	25	25mL	78
115-119	52-54	15 mL	65 mL	39	78	39 mL	26	26	26mL	80
120-124	55-56	15 mL	68 mL	41	82	41 mL	27	27	27mL	83
125-129	57-58	15 mL	71 mL	43	86	43 mL	28	28	28mL	86
130-134	59-60	15 mL	73 mL	44	88	44 mL	29	29	29mL	88
135-139	61-63	15 mL	76 mL	46	92	46 mL	30	30	30mL	91
140-144	64-65	15 mL	80 mL	48	96	48 mL	32	32	32mL	95
145-149	66-67	15 mL	83 mL	50	100	50 mL	33	33	33mL	98
>149	>67	15 mL	85 mL	50	100	50 mL	35	35	35mL	100

1 mg = 1 mL

3-HOUR INFUSION

The recommended dose is 100 mg administered as 60 mg in the first hour, of which 6-7 mg is administered as a bolus over the first 1-2 minutes and the remainder is administered by continuous infusion, 20 mg by continuous infusion during the second hour, and 20 mg by continuous infusion over the following one to four hours. For smaller patients (<65 kg), a dose of 1.25 mg/kg may be warranted. This 3-hour infusion regimen is recommended for use up to 12 hours after onset of AMI symptoms.

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

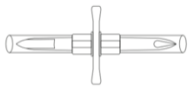
ACTIVASE rt-PA should be reconstituted by aseptically adding 50 mL Sterile Water for Injection, USP [SWFI] to the vial of ACTIVASE rt-PA, . It is important that ACTIVASE rt-PA be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection. 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.

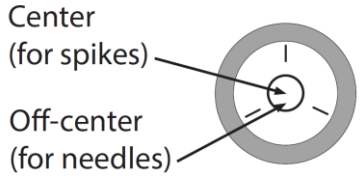
Before further dilution or administration, parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. Because ACTIVASE rt-PA contains no preservatives, it must be used within 8 hours following reconstitution (when stored at 2-30℃) (see STORAGE AND STABILITY).

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.

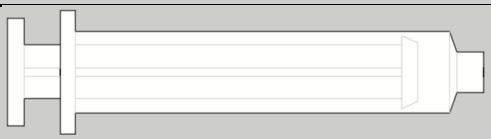
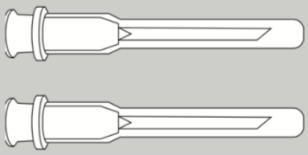
100 MG VIALS

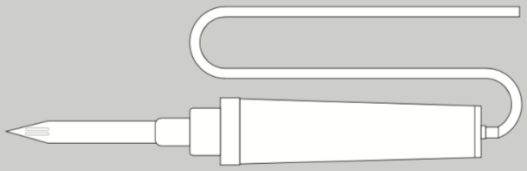
Activase 100 mg Kit Contents

Transfer device	
Activase 100 mg vial (no vacuum)	
Activase 100 mg vial stopper parts:	

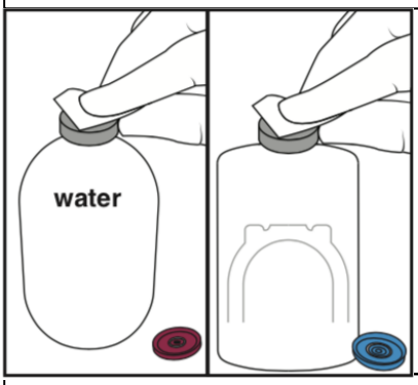
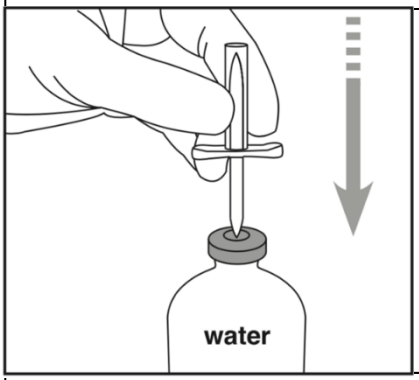
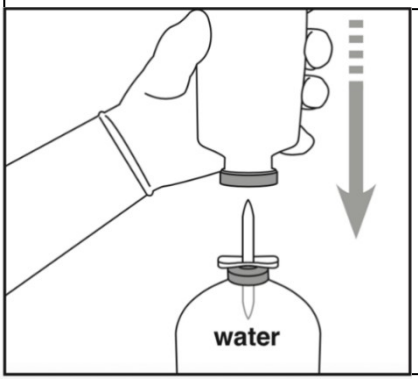
	
Sterile Water for Injection (water) vial Note: Do not use Bacteriostatic Water for Injection, USP.	
Prescribing Information	
Instructions for Use	

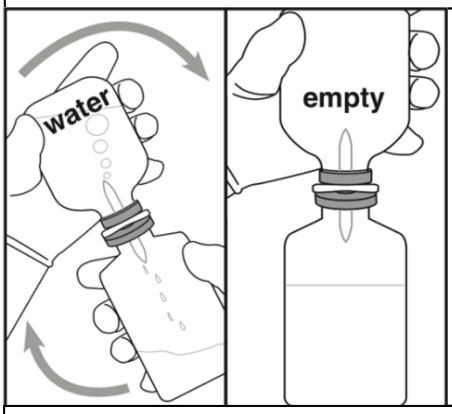
Activase 100 mg Also Required (not included in kit)

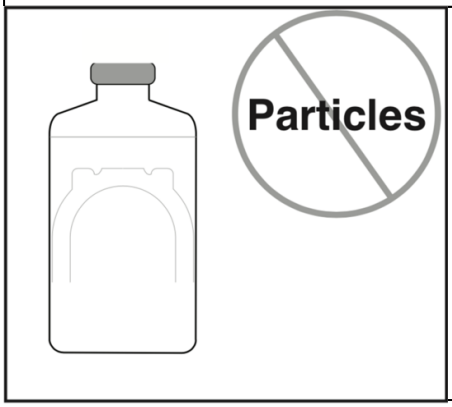
1 Luer syringe for removing bolus dose, as needed	
1 Luer syringe for removing excess volume, as needed	
2 large bore needles	
2 Alcohol swabs	

IV infusion set	

Activase 100 mg Reconstitution (use aseptic technique)

Step 1: Cleaning	
	• Remove caps from both vials. • Wipe both stoppers with alcohol swabs.
Step 2: Spiking Water Vial	
	• 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. **⚠ Do not invert water vial yet. Inverting too early may lead to leakage and incorrect dosing.**
Step 3: Spiking Activase Vial	
	• 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. **⚠ Inserting the spike off-center could lead to stopper collapse.**

Step 4: Inverting and transferring	
	• 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.**
Step 5: Inspecting	

	• Separate empty water vial and transfer device from Activase vial.
	• Reconstituted Activase vial (1 mg/mL) should be:
	  ○ 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

90-MINUTE ACCELERATED INFUSION

The ACTIVASE rt-PA dose administered by accelerated infusion may be prepared and administered as follows:

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

1) By removing 15 mL from the vial of reconstituted (1 mg/mL) ACTIVASE 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.

2) By removing 15 mL from a port (second injection site) on the infusion line after the infusion set

is primed.

3) By programming an infusion pump to deliver a 15 mL (1 mg/mL) bolus at the initiation of the infusion.

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

3-HOUR INFUSION

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

1) By removing 6-10 mL 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.

2) By removing 6-10 mL from a port (second injection site) on the infusion line after the infusion set is primed.

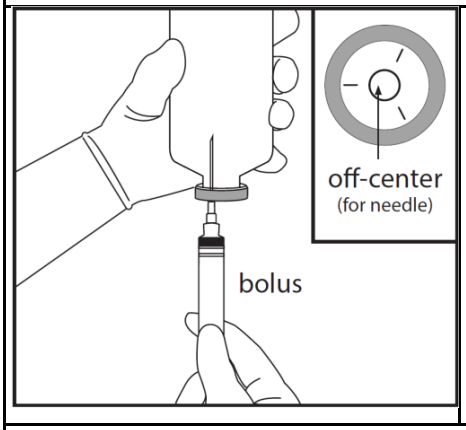
3) By programming an infusion pump to deliver a 6-10 mL (1 mg/mL) bolus at the initiation of the infusion.

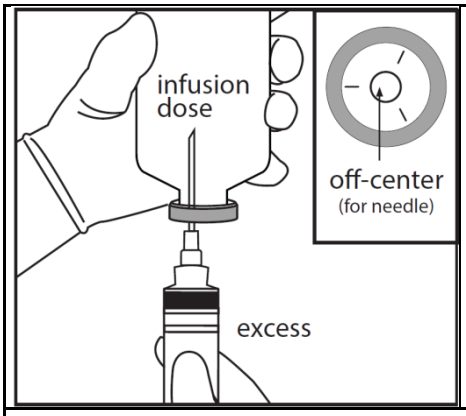
B. The remainder of the ACTIVASE rt-PA dose may be administered using either a polyvinyl chloride bag or glass vial and infusion set.

100 MG VIALS

Activase 100 mg Administration (use aseptic technique)

Administration Warnings	
 **Review important information to the right 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 within center ring of stopper, away from hole made by transfer device.** Insert needle 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 6: Preparing bolus	
	• Check if bolus is needed. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw bolus amount. **Do not push any air from the syringe into vial (may cause leakage).** • 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	

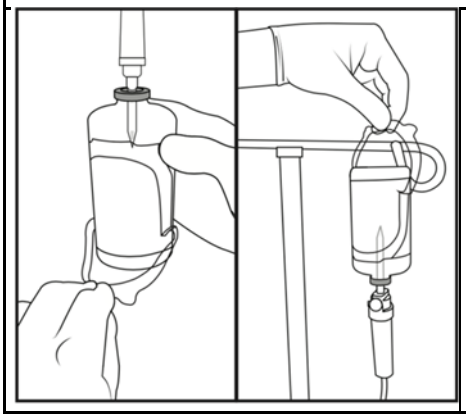


- Check if there is excess volume in vial. If yes, attach needle to empty Luer syringe.
- Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw excess volume.

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

- Discard any excess volume.
- Leave infusion dose in vial.

Step 8: Spiking and hanging



- 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 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

Description
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.

7 WARNINGS AND PRECAUTIONS

General

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

Routine management of myocardial infarction should not be deferred after evidence of successful thrombolysis is seen. Evaluation and management of underlying atherosclerotic heart disease should be carried out as clinically indicated.

Non compressible 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.

Bleeding

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)

The concomitant use of heparin anticoagulation contributes to the risk of bleeding.

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).

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 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 ≥ 175 mm Hg and/or diastolic BP ≥ 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.

In a small subgroup of AMI patients who are at low risk for death from cardiac causes (i.e., no previous myocardial infarction, Killip class I) and who have high blood pressure at the time of presentation, the risk for stroke may offset the survival benefit produced by thrombolytic therapy.

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.

Cardiovascular

Arrhythmias
Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE rt-PA are administered.

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.

Use of Antithrombotics

Acetylsalicylic acid (ASA) and heparin may be administered concomitantly with and following infusions of ACTIVASE rt-PA. Because heparin, ASA or ACTIVASE rt-PA alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Immune

Hypersensitivity
Anaphylactoid reactions associated with the administration of Activase 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.

Angioedema
Angioedema has been observed in post-market experience in patients treated for acute myocardial infarction (see DRUG INTERACTIONS and ADVERSE REACTIONS: Hypersensitivity). 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.

Readministration

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

Pregnant Women

ACTIVASE has been shown to have an embryocidal effect in rabbits when intravenously administered in doses of approximately two times (3 mg/kg) the human dose for AMI. No maternal or fetal toxicity was evident at 0.65 times (1 mg/kg) the human dose in pregnant rats and rabbits dosed during the period of **organogenesis**. There are no adequate and well controlled studies in pregnant women. ACTIVASE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether ACTIVASE rt-PA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE rt-PA is administered to a nursing woman.

Pediatrics

Safety and effectiveness of ACTIVASE rt-PA in children has not been established. Therefore, treatment of such patients is not recommended.

Geriatrics

The risks of therapy may be increased in the elderly (see ADVERSE REACTIONS, ACTIONS AND CLINICAL PHARMACOLOGY).

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.[13,22,23] 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)

Hypersensitivity
Hypersensitivity reactions, e.g. anaphylactoid reaction, anaphylactic reaction, laryngeal edema, angioedema, rash urticaria and shock have been reported very rarely (<0.02%). A cause and effect relationship has not been established. A rare fatal outcome for hypersensitivity has been reported.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Reported Incidence of Bleeding During ACTIVASE Treatment

The incidence of all strokes reported for the accelerated (90 minute) infusion regimen in the GUSTO trial was 1.6%, while the incidence of nonfatal stroke was 0.9%. The incidence of hemorrhagic stroke was 0.7%, not all of which were fatal. Data from previous trials utilizing a three hour infusion indicates that the incidence of total stroke in six randomized double-blind placebo controlled trials was 1.2% (37/3161) in ACTIVASE rt-PA-treated patients (≤100 mg) compared with 0.9% (27/3092) in placebo-treated patients.

Although the incidence of all strokes, as well as that for hemorrhagic stroke, increased with increasing age, treatment with accelerated regimen of ACTIVASE rt-PA was still shown to reduce mortality in older patients. For patients who were over 75 years of age, a predefined subgroup consisting of 12% of patients enrolled, the incidence of stroke was 4.0% for the accelerated regimen of ACTIVASE rt-PA group, 2.8% for streptokinase (intravenous heparin), and 3.2% for streptokinase (subcutaneous heparin) (See Table 1). However, combined 30-day mortality or non-fatal stroke was 20.6% for accelerated regimen of ACTIVASE rt-PA, 21.5% for streptokinase (intravenous heparin) and 22.0% for streptokinase (subcutaneous heparin) in the GUSTO study.

Table 1

	rt-PA	SK (IV)		SK (SQ)	
	%	%	p-value	%	p-value
stroke	1.6%	1.4%	0.32	1.2%	0.03
intracranial hemorrhage	0.7%	0.6%	0.22	0.5%	0.02
stroke in >75 yrs	4.0%	2.8%	0.09	3.2%	0.27
intracranial hemorrhage >75 yrs	2.0%	1.1%	0.06	1.3%	0.17

p-value is for pairwise comparison to rt-PA.

The following incidence of significant internal bleeding (estimated as ≥ 250 mL blood loss) has been reported in studies involving over 1300 patients treated at all doses of ACTIVASE rt-PA, administered as a 3-hour infusion regimen:

- gastrointestinal 5%

- genitourinary 4%

The following incidence of moderate or severe bleeding was reported when ≤100 mg ACTIVASE rt-PA was administered by accelerated infusion to >10,000 patients [GUSTO study]:

- gastrointestinal 1.5%
- genitourinary 0.5%

The incidence of intracranial bleeding in patients treated with up to 120 mg ACTIVASE rt-PA (3-hour infusion) has been 0.4%. At doses in excess of 120 mg (120-180 mg) the incidence of intracranial bleeding increased to 1.3%. The incidence of intracranial bleeding in patients treated with ≤100 mg ACTIVASE rt-PA (accelerated infusion, weight adjusted) was 0.7%. The maximum total dose of ACTIVASE rt-PA used in the treatment of acute myocardial infarction should not exceed 100 mg.

Death and permanent disability have been reported in patients who have experienced stroke and other serious bleeding episodes.

8.3 Less Common Clinical Trial Adverse Reactions

Not applicable.

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

Not applicable.

8.5 Post-Market Adverse Reactions

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

Patients with myocardial infarction can experience disease-related events such as cardiogenic shock, arrhythmias, AV block, pulmonary edema, heart failure, cardiac arrest, recurrent ischemia, myocardial reinfarction, myocardial rupture, mitral regurgitation, pericardial effusion, pericarditis, cardiac tamponade, venous thrombosis and embolism, and electromechanical dissociation. These events may lead to death. Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever.

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 ADVERSE REACTIONS OVERVIEW: Hypersensitivity section).

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.

An occlusive thrombus is present in the infarct-related coronary artery in approximately 80% of patients experiencing a transmural myocardial infarction evaluated within four hours of onset of symptoms.

Detailed Pharmacology

Effect on Coagulation

ACTIVASE rt-PA (alteplase for injection) differs from other plasminogen activators in that it is fibrin dependent. Relatively selective fibrinolysis with ACTIVASE rt-PA, i.e., localized activation of the fibrinolytic system, is possibly due to several factors such as the high affinity of tissue plasminogen activator for fibrin, the fibrin-dependent activation of tissue plasminogen activator, and the coprecipitation of plasminogen within the fibrin clot. As a result, ACTIVASE rt-PA produces clot dissolution in vivo with minimal systemic effects.

Two controlled trials in acute myocardial infarction patients have measured circulating plasma fibrinogen levels after infusion of activators. Results with ACTIVASE rt-PA were compared to those with a non-selective activator, streptokinase. In the first study, the circulating fibrinogen level (measured by coagulation rate assay) was approximately 61% of the starting value in ACTIVASE rt-PA treated patients compared with approximately 12% for those treated with streptokinase. In the second study, post-treatment levels of fibrinogen (measured by the sodium phosphate precipitation method) were approximately 75% of baseline with ACTIVASE rt-PA compared with 53% with streptokinase.

In a dose response trial conducted by the National Heart, Lung and Blood Institute (NHLBI), comparing three different doses of ACTIVASE rt-PA in AMI patients, baseline plasma fibrinogen levels (measured by the precipitation method 1-2 hours after infusion) were 96%, 90% and 77% for doses of 80 mg, 100 mg, and 150 mg respectively.

In general, it is believed that fibrinogen levels in excess of about 100 mg per decilitre may be important in controlling most occurrences of bleeding. In two multicentre trials of ACTIVASE rt-PA in AMI patients in which degradation of circulating fibrinogen was measured, the incidence of fibrinogen levels below 100 mg% (mg/dL ~ measured with precipitation techniques) was less than 5%. In two multicentre trials of ACTIVASE rt-PA in AMI patients, the incidence of fibrinogen levels below 100 mg% (measured with clotting rate techniques) was less than 25%. In contrast, a multicentre trial comparing ACTIVASE rt-PA to streptokinase found the incidence of fibrinogen levels below 100 mg% in the streptokinase group (measured with clotting rate techniques) to be 95%.

Another measure of systemic fibrinolytic activation is the elevation of fibrinogen-fibrin degradation products (FDP's). In a study in AMI patients comparing ACTIVASE rt-PA to streptokinase, FDP's increased to 0.75 mg/mL in the streptokinase group but to only 0.10 mg/mL in the ACTIVASE rt-PA group.

Myocardial Infarction Studies

In angiographically controlled studies, intravenous ACTIVASE rt-PA has been demonstrated to induce prompt and significant improvement in perfusion of the obstructed coronary vessel. In a study sponsored by the National Heart, Lung and Blood Institute designed to compare the intravenous thrombolytic effects of ACTIVASE rt-PA and streptokinase, The Thrombolysis in Myocardial Infarction (TIMI) trial which involved 316 patients at 13 centres, ACTIVASE rt-PA produced reperfusion in 66% of patients, compared with 36% for streptokinase treated patients studied angiographically 90 minutes after the commencement of thrombolytic therapy. In a subsequent non-comparative phase of the same study which involved 139 patients, ACTIVASE rt-PA produced reperfusion in 73% of patients who received at least 70 - 100 mg over 90 minutes. A second randomized study, The European Cooperative Trial, demonstrated similar efficacy of intravenous ACTIVASE rt-PA.

The recanalization rate for a 70 mg dose is equivalent to that for a 100 mg dose at 90 minutes, but the 100 mg dose elicits thrombolysis more rapidly. The following table summarizes the results of the TIMI open label dose response study:

PERCENT VESSELS OPEN		
Time after onset of infusion	**Dose in first 90 minutes**	
	70 mg	**100 mg**
30 min.	24%	42%
60 min.	57%	68%
90 min.	71%	76%
No. of patients	83	62

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. There is no difference in the dominant initial plasma half-life between the 3-hour and accelerated regimens for acute myocardial infarction (AMI). 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: alteplase for injection

Chemical name: alteplase

Molecular formula and molecular mass:

The theoretical mass of rt-PA is 65,000 Daltons.

The amino acid sequence is as shown in Figure 1 & Figure 2

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).

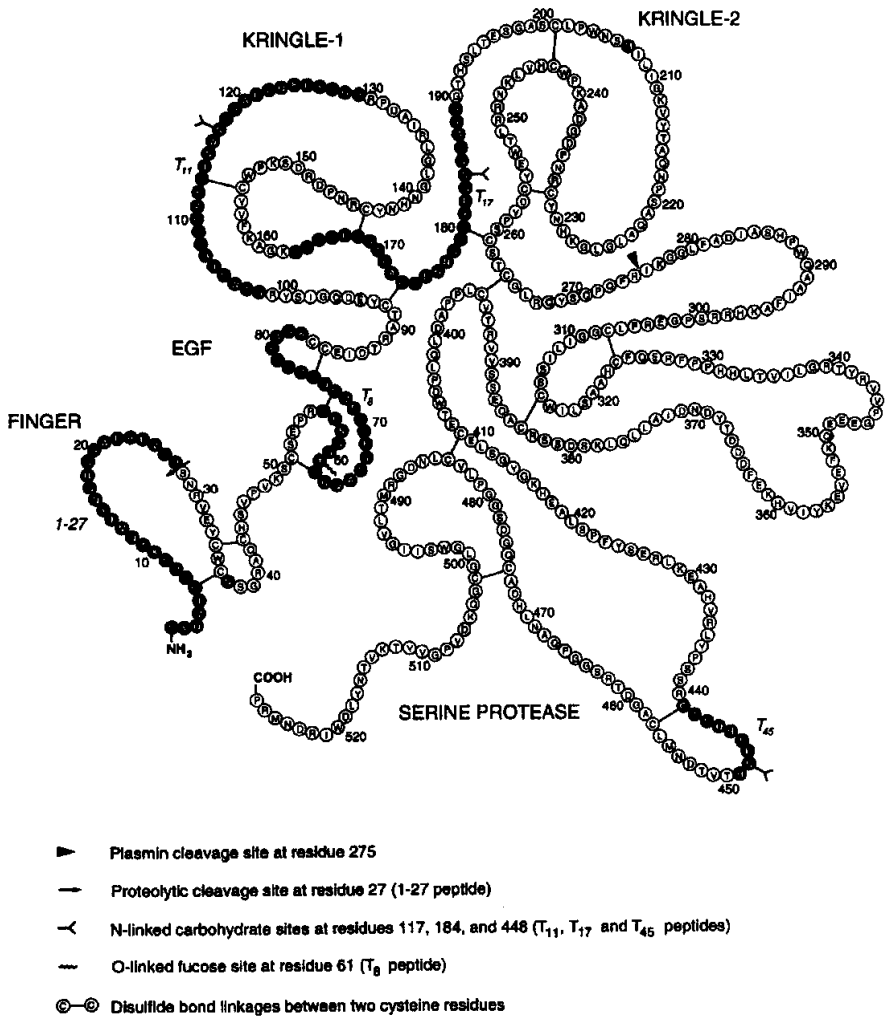


FIGURE 2

rt-PA (527 res.)

SYQVICRDEKTQMIYQQHQSWLRPVLRSNRVEYCWCNSGRAQCHSVPVKSCSEPRCFNG

GTCQQALYFSDFVCQCPEGFAGKCCEIDTRATCYEDQGISYRGTWSTAESGAECTNWNSS

ALAQKPYSGRRPDAIRLGLGNHNYCRNPDRDSKPWCYVFKAGKYSSEFCSTPACSEGNSDC

YFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAK

PWCHVLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQAAIFAKHRRS

PGERFLCGGILISSCWILSAAHCFQERFPPHHLTVILGRTYRVVPGEEEQKFEVEKYIVHKEFD

DDTYDNDIALLQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSE

RLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSGGPLVCLN

DGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNMRP

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 rt-PA is expressed as a 59kD protein. The addition of carboyhydrate 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 Clinical Trials by Indication

Acute Myocardial Infarction

Acute Myocardial Infarction Patients Studies

Two ACTIVASE rt-PA dose regimens have been studied in patients experiencing AMI: accelerated infusion, and 3-hour infusion. The comparative efficacy of these two regimens has not been evaluated.

There is no difference in the dominant initial plasma half-life between the 3-hour and accelerated regimens for acute myocardial infarction (AMI).

GUSTO Trial – 90 Minute Accelerated Infusion

90-Minute Accelerated Infusion in Patients with Acute Myocardial Infarction Accelerated infusion of ACTIVASE rt-PA was studied in an international, multi-centre trial (GUSTO) where 41,021 patients with acute myocardial infarction were randomized to four thrombolytic regimens: accelerated infusion of ACTIVASE rt-PA (< 100 mg over 90 minutes) plus intravenous heparin; streptokinase (1.5×10^6 units over 60 minutes) plus intravenous heparin; streptokinase (1.5×10^6 units over 60 minutes) plus subcutaneous heparin; or combined ACTIVASE rt-PA (1.0 mg/kg over 60 minutes) plus streptokinase (1.0×10^6 units over 60 minutes). Acetylsalicylic acid (ASA) was administered daily. The results are shown in Table 2.

The 30-day mortality for the accelerated infusion of ACTIVASE rt-PA was 1% lower (14% relative risk reduction) than for streptokinase (intravenous or subcutaneous heparin). In addition, the combined incidence of 30-day mortality or non-fatal stroke for accelerated ACTIVASE rt-PA was 1% lower (12% relative risk reduction) than for streptokinase (intravenous heparin) and 0.8% lower (10% relative risk reduction) than for streptokinase (subcutaneous heparin). One-year follow-up data suggest a sustained mortality benefit. Subgroup analysis of patients by age, infarct location, and time from symptom onset to thrombolytic treatment showed consistently lower 30-day mortality for the group receiving the accelerated infusion of ACTIVASE rt-PA. For patients who were over 75 years of age, a predefined subgroup consisting of 12% of patients enrolled, the incidence of stroke was 4.0% for the group receiving the accelerated infusion of ACTIVASE rt-PA, 2.8% for streptokinase (intravenous heparin), and 3.2% for streptokinase (subcutaneous heparin); the incidence of combined 30-day mortality or nonfatal stroke was 20.6% for accelerated infusion of ACTIVASE rt-PA, 21.5% for streptokinase (intravenous heparin), and 22.0% for streptokinase (subcutaneous heparin).

3-Hour Infusion in Patients with Acute Myocardial Infarction

In patients studied with coronary angiography prior to and following infusion of ACTIVASE rt-PA, the use of ACTIVASE rt-PA resulted in reperfusion of documented obstructed vessels within 90 minutes after the commencement of thrombolytic therapy in approximately 70% of patients. In two studies involving 145 patients, ACTIVASE rt-PA produced reperfusion in 73% of patients who received 70-100 mg (40.6 to 58×10^6 I.U.) over 90 minutes. In two double blind randomized controlled trials in patients with AMI, the patients infused with 80-100 mg of ACTIVASE rt-PA experienced improved ventricular function and reduced incidence of clinical congestive heart failure compared to those treated with placebo.

In a double-blind study involving 5013 patients (ASSET Study) where patients were infused with either ACTIVASE rt-PA or placebo within 5 hours of onset of symptoms of AMI, improved 30-day survival was shown in patients receiving ACTIVASE rt-PA compared to placebo. At one month, the overall mortality rates were 7.2% for the ACTIVASE rt-PA-treated group and 9.8% for the placebo-treated group (p=0.001). This benefit was maintained at 6 months (10.4% and 13.1% for ACTIVASE rt-PA and placebo-treated patients respectively, p=0.008).

In the LATE study involving 5711 patients where patients were infused with either alteplase (100 mg over 3 hours) or placebo within 6-24 hours of onset of AMI symptoms, the 35-day mortality rates were 8.9% for ACTIVASE rt-PA treated patients and 10.3% for placebo-treated patients (p=not significant). Pre-specified survival analysis according to treatment within 12 hours of symptom onset showed a significant reduction in mortality for the ACTIVASE rt-PA treated patients, 8.9% versus 12.0% for the placebo treated patients (p=0.0229).

Study Results

Table 2 – Results from GUSTO Trial

EVENT	ACCELERATED ACTIVASE RT-PA (IV HEPARIN)	STREPTOKINASE (IV HEPARIN)	P-VALUE*	STREPTOKINASE (SC HEPARIN)	P-VALUE*
30-Day Mortality	6.3%	7.3%	0.003	7.3%	0.007
30-Day Mortality or Nonfatal Stroke	7.2%	8.2%	0.006	8.0%	0.036
24-Hour Mortality	2.4%	2.9%	0.009	2.8%	0.029

*Two-tailed p-value is for comparison of accelerated infusion of ACTIVASE rt-PA to the respective streptokinase control arm.

In-hospital events in the overall patient population, as well as events in patients who survived beyond 30 days are shown in Table 3.

Table 3 In-Hospital Clinical Events/Procedures[1]

	OVERALL			30-DAY SURVIVORS[2]		
	SK (POOLED) %		ACTIVASE %	SK (POOLED) %		ACTIVASE%
Reinfarction	3.9		4.1	3.4		3.6
Cardiogenic Shock	6.5	***	5.0	3.2	***	2.3
CABG	8.3		9.0	8.6		9.2
PTCA (IRA)[3]	14.3		14.6	14.8		15.2
CHF or Pulmonary Edema	16.7	***	15.0	14.3	**	13.1
Recurrent Ischemia	20.3		19.7	20.1		19.6
Sustained Hypotension	12.8	***	10.0	9.4	***	7.0
2E or 3E Atrio-Ventricular Block	8.9	***	7.3	7.6	***	6.2

Ventricular Tachycardia	6.5	*	5.7	4.8		4.4
Ventricular Fibrillation	6.9	*	6.2	5.0		4.6
Asystole	6.0	**	5.1	1.9		1.7
Atrial Fibrillation/Flutter	9.9	**	8.7	9.1	**	8.0
Acute Mitral Regurgitation	1.5		1.3	1.3		1.1
Swan-Ganz Catheter	12.6	**	11.5	11.5		10.7
Cardioversion	9.8	**	8.6	7.4	*	6.7
Angiography	55	*	56.5	57.4	*	58.9

[1] Events other than death, stroke and bleeding.
[2] Patients alive at 30-day timepoint
[3] IRA=Infarct-Related Artery
*p<0.05, **p<0.01, ***p<0.001

An angiographic substudy of the GUSTO trial provided data on infarct-related artery patency. Results are shown in Table 4. Reocclusion rates were similar for all three treatment regimens.

Table 4

Patency	Accelerated ACTIVASE rt-PA			Streptokinase (IV heparin)			Streptokinase (SC heparin)		
	TIMI 2 or 3	TIMI 3	(N)	TIMI 2 or 3	TIMI 3	(N)	TIMI 2 or 3	TIMI 3	(N)
90-Minute	81.3% *	54.8% *	(272)	59.0%	30.7%	(261)	53.5%	27.3%	(260)
180-Minute	76.3%	41.3%	(80)	72.4%	38.2%	(76)	71.6%	34.7%	(95)
24 Hour	88.9%	39.5%	(81)	87.5%	47.2%	(72)	82.1%	56.7%	(67)
5-7 Day	83.3%	63.9%	(72)	90.9%	67.5%	(77)	78.7%	58.7%	(75)

* p<0.001 compared to streptokinase with IV heparin and SC heparin. No other treatment groups significantly different.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The safety of the pharmacological administration of rt-PA was evaluated by conducting acute and sub-acute 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.

1) 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

2) 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.

3) 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.

4) 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**.

What is ACTIVASE rt-PA used for?

ACTIVASE rt-PA (alteplase for injection) is indicated for intravenous use in adults for:

- the breakdown of suspected occlusive coronary artery clots associated with evolving transmural myocardial infarction; and
- the reduction of death associated with Acute Myocardial Infarction (AMI), the improvement of function of the heart following AMI and the reduction in occurrence of congestive heart failure.

How does ACTIVASE rt-PA work?

ACTIVASE rt-PA when introduced into the systemic circulation, will bind to fibrin (protein that impedes the flow of blood) in blood clots and converts the entrapped plasminogen to plasmin (which breakdowns 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:

- Hypersensitivity to alteplase or to any ingredient in the formulation or components of the container
- Bleeding disorder or history of bleeding
- History of stroke
- Patients receiving other intravenous blood thinners
- Recent major surgery or trauma
- Brain tumour, abnormality of the blood vessels, or aneurysm
- Uncontrolled high blood pressure (i.e., > 180 mm Hg systolic or >110 mm Hg diastolic)
- Recent traumatic cardiopulmonary resuscitation

The most common complication encountered during therapy with ACTIVASE rt-PA (alteplase for injection) is bleeding. Using heparin anticoagulation with ACTIVASE rt-PA contributes to the risk of bleeding.

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 are/have/had:

- 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)
- A 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 medication that affects blood clotting (i.e., warfarin sodium)
- Use of blood clot dissolving drugs
- Cholesterol embolization

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)

How to take ACTIVASE rt-PA:

ACTIVASE rt-PA (alteplase for injection) is intended for intravenous use only administered by a trained Health Care Professional.

Recommended Dose and Dosage Adjustment

There are two dose regimens for ACTIVASE rt-PA for use in the management of AMI.

90-Minute Accelerated Infusion

The recommended total dose is based upon patient weight, not to exceed 100 mg.

- For patients weighing >67 kg, the recommended dose is 100 mg, administered as a 15 mg intravenous bolus, followed by 50 mg infused over 30 minutes and then 35 mg infused over the next 60 minutes.

- For patients weighing < 67 kg, the recommended dose is 15 mg administered as an intravenous bolus, followed by 0.75 mg/kg to a maximum of 50 mg, infused over the next 30 minutes, and then 0.50 mg/kg to a maximum of 35 mg infused over the next 60 minutes.

This 90-minute infusion regimen is recommended for use up to 6 hours after onset of AMI symptoms.

3-Hour Infusion

The recommended dose is 100 mg administered as 60 mg in the first hour, of which 6-7 mg is administered as a bolus over the first 1-2 minutes and the remainder is administered by continuous infusion, 20 mg by continuous infusion during the second hour, and 20 mg by continuous infusion over the following one to four hours.

For smaller patients (<65 kg), a dose of 1.25 mg/kg may be warranted. This 3-hour infusion regimen is recommended for use up to 12 hours after onset of AMI symptoms.

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.

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

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.

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)
- Nausea and/or vomiting, low blood pressure and fever
- Patients with myocardial infarction can experience disease-related events that may lead to death.

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			
Gastrointestinal bleeding (5%)		✓	
Genitourinary bleeding (urinary tract) (4%)		✓	
Intracerebral hemorrhage (bleeding within the skull) (1.3%)		✓	
UNKNOWN			
Internal bleeding involving lungs		✓	
Thromboembolism		✓	
Cholesterol embolism		✓	

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.

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

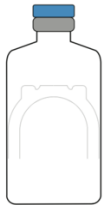
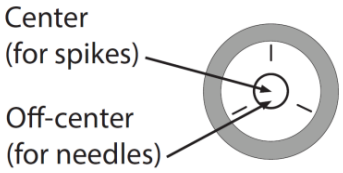
contacting the sponsor Hoffmann-La Roche Limited at: 1-888-762-4388).

This leaflet was prepared by Hoffmann-La Roche Limited.

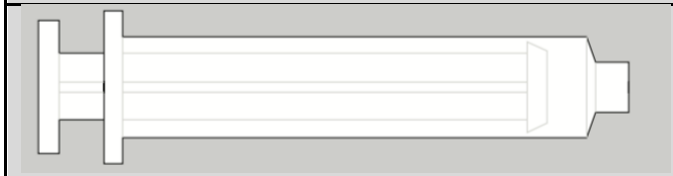
Last Revised: June 26, 2024

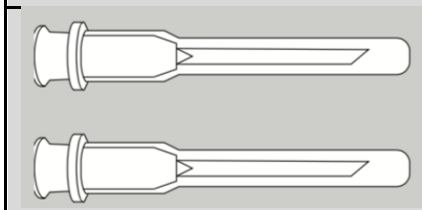
Activase®
(alteplase)
for infusion
100 mg (58 million IU)

Read before preparing Activase®
Instructions for Use
See package insert for full prescribing information

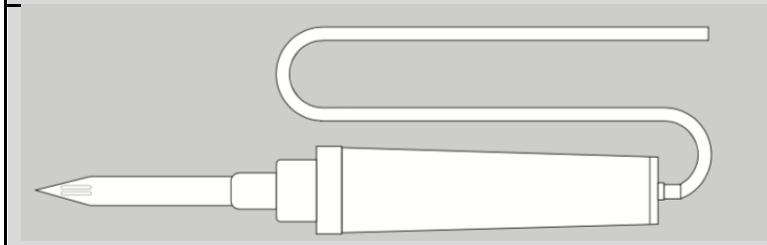
Activase® (alteplase)	
Kit Contents	
Transfer device	
Activase vial (no vacuum)	
Activase vial stopper parts: 	

Sterile Water for Injection (water) vial Note: Do not use Bacteriostatic Water for Injection, USP.	
Prescribing Information	
Instructions for Use	

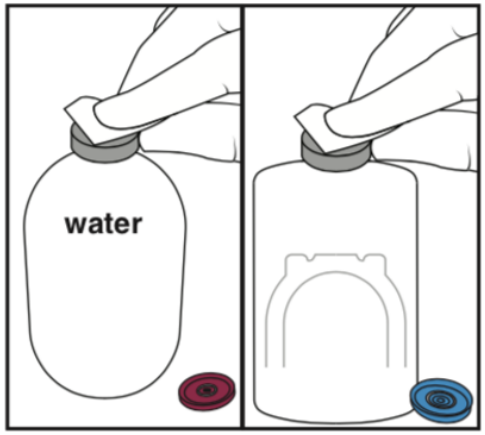
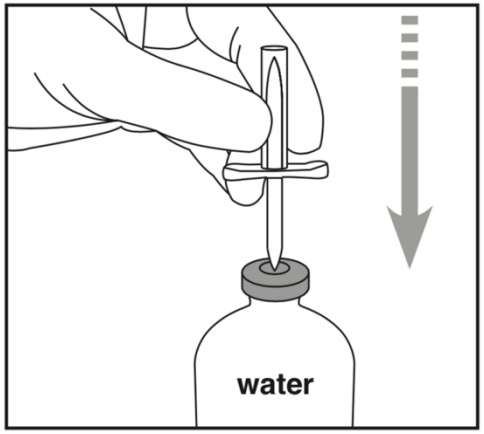
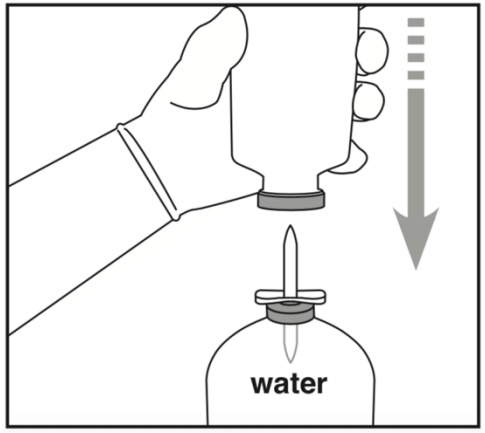
Activase® (alteplase)
Also Required
(not included in kit)
1 Luer Syringe for removing bolus dose, as needed

1 Luer syringe for removing excess volume, as needed

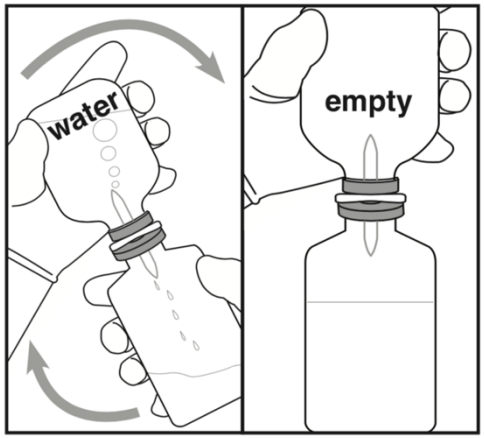
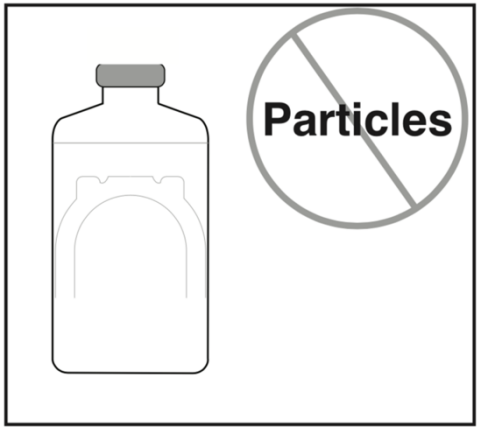
2 large bore needles

2 Alcohol swabs

IV infusion set

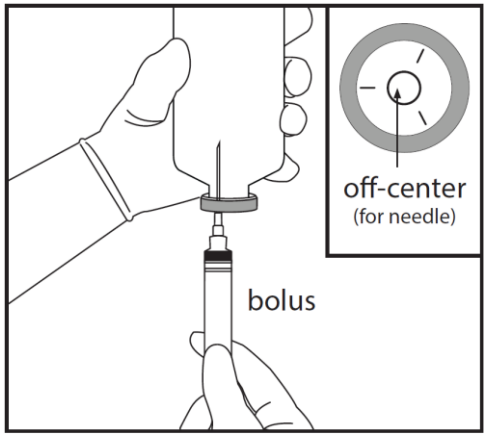
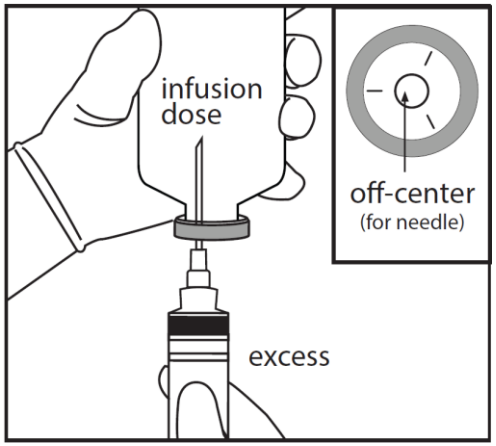
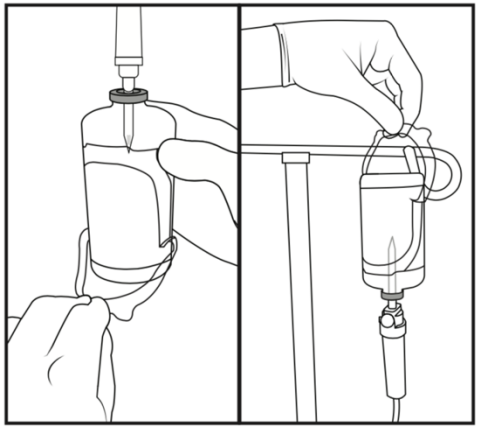


Activase® (alteplase)	**Activase®** (alteplase)	**Activase®** (alteplase)

Reconstitution (use aseptic technique)		
Step 1: Cleaning	**Step 2: Spiking Water vial**	**Step 3: Spiking Activase vial**
		
• Remove caps from both vials. • Wipe both stoppers with alcohol swabs.	• 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. **Do not invert water vial yet. Inverting too early may lead to leakage and incorrect dosing.**	• 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. **Inserting the spike off-center could lead to stopper collapse.**

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 within center ring of stopper, away from hole made by transfer device.
		
		Insert needle 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.

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

• Check if bolus is needed. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw bolus amount. **Do not push any air from syringe into vial (may cause leakage).** • Alternatively, the bolus can be left in the vial and administered via an infusion pump or removed from a port on the infusion line.	• Check if there is excess volume in vial. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw excess volume. **Do not push any air from syringe into vial (may cause leakage).** • Discard any excess volume. • Leave infusion dose in vial.	• 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 clear plastic hanger from vial label. • Hang on IV pole and administer per facility protocol.

Administration Notes
• 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.
Storage & Stability
• 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).

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ACTIVASE® 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
7070 Mississauga Road
Mississauga, Ontario
L5N 5M8

Date of Initial Authorization:
DEC 31,1996

Date of Revision:
June 26, 2024

Submission Control Number: 285964

RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.3 Reconstitution	04/2024
4 Dosage and Administration, 4.4 Administration	04/2024

TABLE OF CONTENTS

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

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/mm^3

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 (≤ 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.

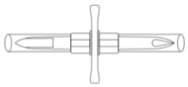
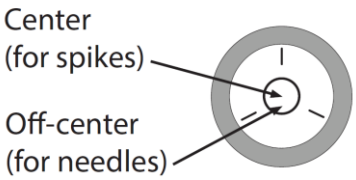
Before further dilution or administration, parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. Activase contains no antibacterial preservatives and must be used within 8 hours following reconstitution (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.

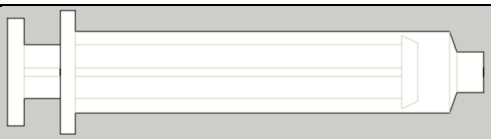
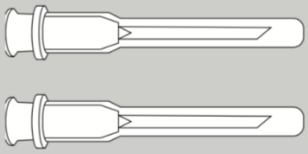
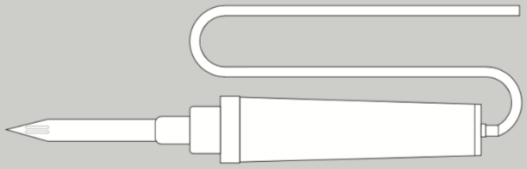
100 MG VIALS

Activase 100 mg Kit Contents

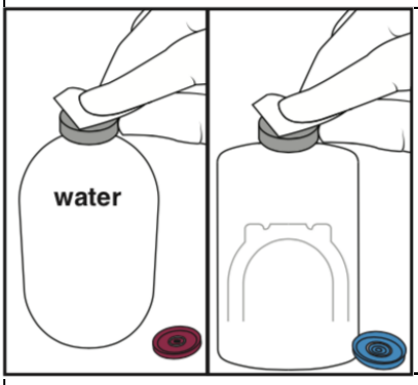
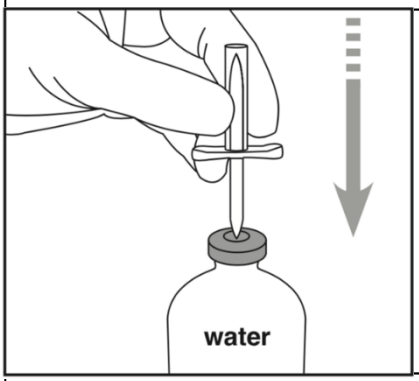
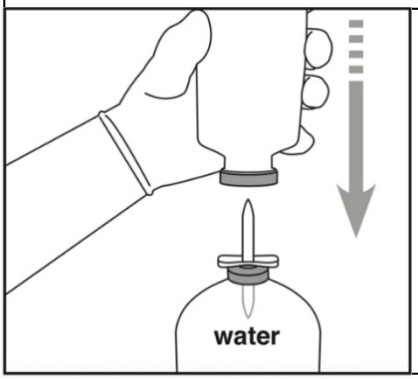
Transfer device	
Activase 100 mg vial (no vacuum)	
Activase 100 mg vial stopper parts:	
Sterile Water for Injection (water) vial Note: Do not use Bacteriostatic Water for Injection, USP.	
Prescribing Information	
Instructions for Use	

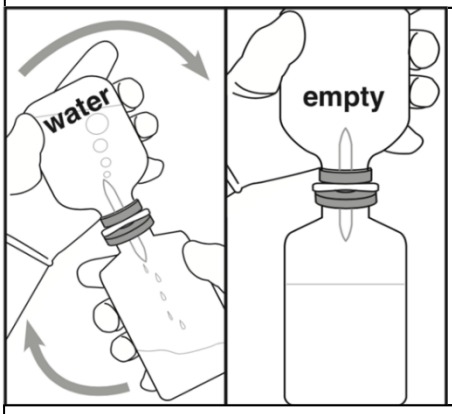
Activase 100 mg Also Required (not included in kit)

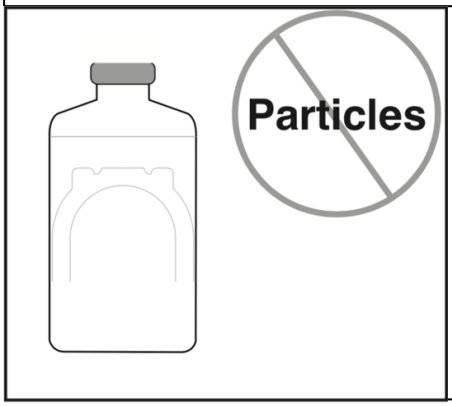
1 Luer syringe for removing bolus dose, as needed	

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	
	• Remove caps from both vials. • Wipe both stoppers with alcohol swabs.
Step 2: Spiking Water Vial	
	• 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. **Do not invert water vial yet. Inverting too early may lead to leakage and incorrect dosing.**
Step 3: Spiking Activase Vial	
	• 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. **Inserting the spike off-center could lead to stopper collapse.**

Step 4: Inverting and transferring	
	• 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.**
Step 5: Inspecting	

	• Separate empty water vial and transfer device from Activase vial.
	• Reconstituted Activase vial (1 mg/mL) should be:
	  ○ 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:

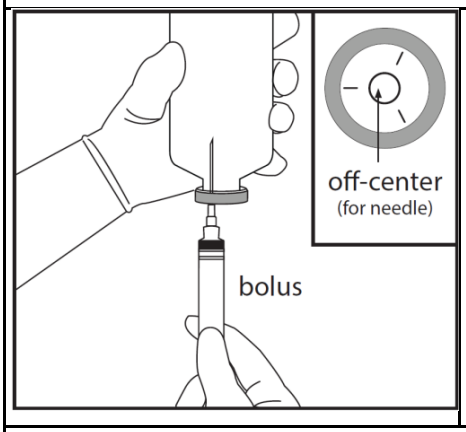
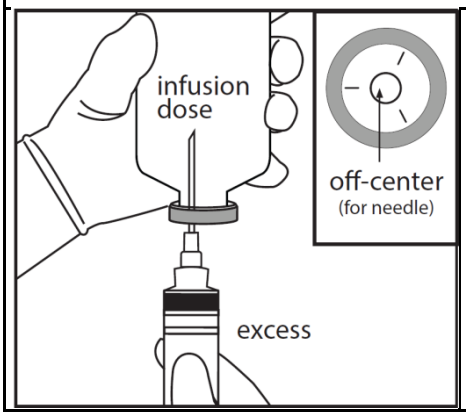
- By removing the appropriate volume from the vial of reconstituted (1-mg/mL) ACTIVASE rt-PA using a syringe and needle. The syringe should not be primed with air and the needle should be inserted into the ACTIVASE rt-PA vial stopper.
- By removing the appropriate volume from a port (second injection 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.

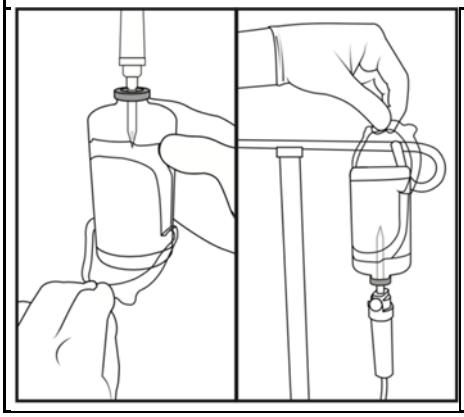
The remainder of the ACTIVASE rt-PA dose may be administered using either a polyvinyl chloride bag or glass vial and infusion set.

100 MG VIALS

Activase 100 mg Administration (use aseptic technique)

Administration Warnings	
 **Review important information to the right 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 within center ring of stopper, away from hole made by transfer device.** Insert needle 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 6: Preparing bolus	
 	• Check if bolus is needed. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw bolus amount. **Do not push any air from the syringe into vial (may cause leakage).** • 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	
 	• Check if there is excess volume in vial. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw excess volume. **Do not push any air from syringe into vial (may cause leakage).** • Discard any excess volume. • Leave infusion dose in vial.

Step 8: Spiking and hanging	
	• 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 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, intraveneous corticosteriods 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

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.

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.

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.

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

[1]Within trial follow-up period. Symptomatic ICH was defined as the occurrence of sudden clinical worsening followed by subsequent verification of ICH on CT scan. Asymptomatic ICH was defined as ICH detected on a routine repeat CT scan without preceding clinical worsening.

[2]Fisher'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%)	54 (17.3%)	p-Value 0.36
0-10	9/99 (9.1%)	2/110 (1.8%)	5.40 (1.14, 25.63)[a]
11-20	26/136 (19.1%)	22/139 (15.8%)	1.26 (0.67, 2.35)
>20	29/77 (37.7%)	30/63 (47.6%)	0.67 (0.34, 1.31)

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 α2-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

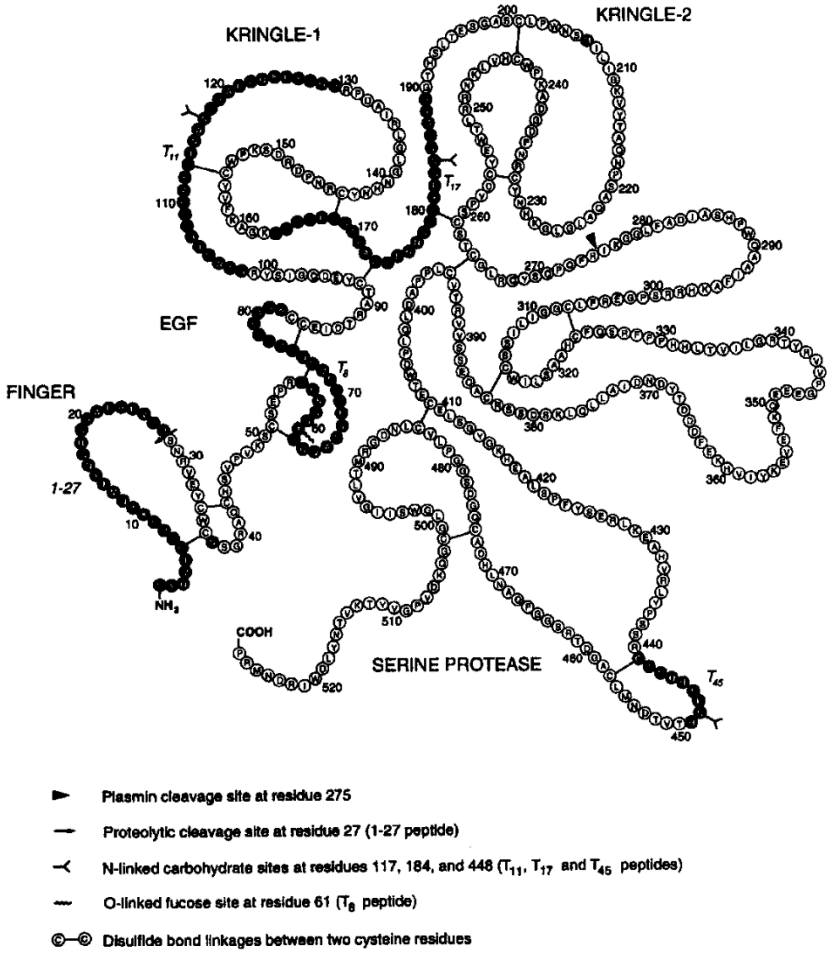


FIGURE 2

rt-PA (527 res.)

SYQVICRDEKTQMIYQQHQSWLRPVLRSNRVEYCWCNSGRAQCHSVPVKSCSEPRCFNG

GTCQQALYFSDFVCQCPEGFAGKCCEIDTRATCYEDQGISYRGTWSTAESGAECTNWNSS

ALAQKPYSGRRPDAIRLGLGNHNYCRNPDRDSKPWCYVFKAGKYSSEFCSTPACSEGNSDC

YFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAK

PWCHVLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSP

GERFLCGGILISSCWILSAAHCFQERFPPHHLTVILGRTYRVVPGEEEQKFEVEKYIVHKEFDD

DTYDNDIALLQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERL

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 carboyhydrate 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 Clinical Trials by Indication

Acute Ischemic Stroke

NINDS Study Summary

The National Institute of Neurological Disorders and Stroke (NINDS) acute ischemic stroke study[31] 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.

Study Results

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

	Frequency of Favourable Outcome[1]		
	Placebo	ACTIVASE rt-PA	Absolute Difference
Analysis	(n=165)	(n=168)	(95% CI)
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)

[1]Favourable 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% Cl, 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., $\geq$ 175 mm Hg systolic and/or $\geq$ 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:

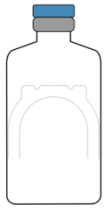
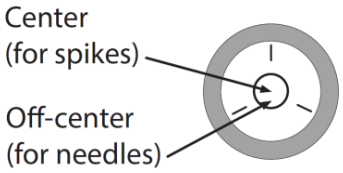
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; 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

Last Revised: June 26, 2024

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

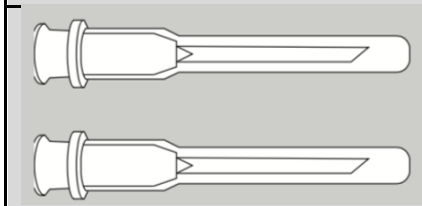
Read before preparing Activase®
Instructions for Use
See package insert for full prescribing information

Activase® (alteplase)	
Kit Contents	
Transfer device	
Activase vial (no vacuum)	
Activase vial stopper parts: 	

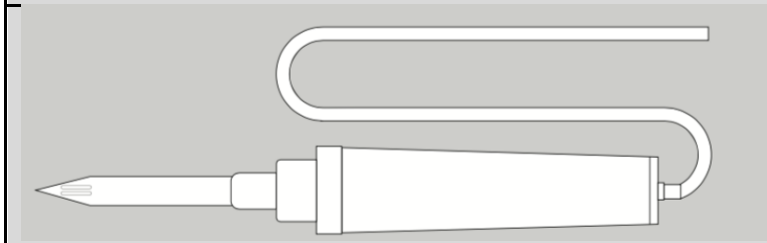
Sterile Water for Injection (water) vial Note: Do not use Bacteriostatic Water for Injection, USP.	
Prescribing Information	
Instructions for Use	

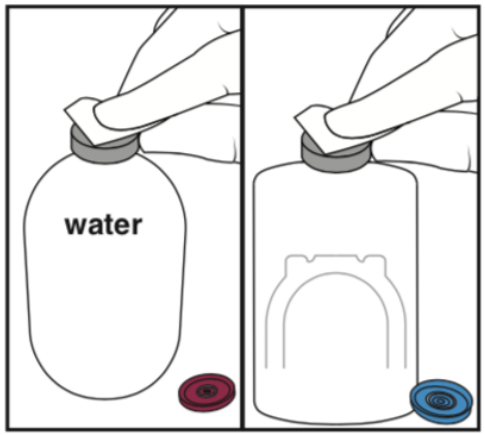
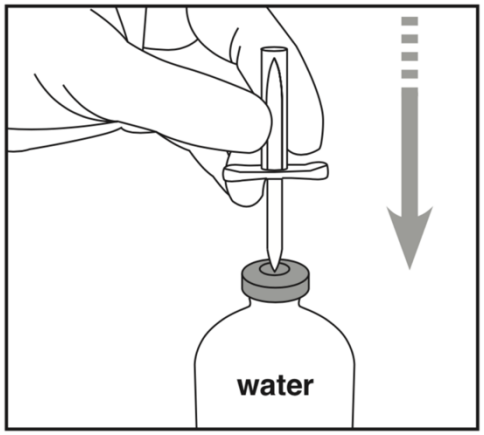
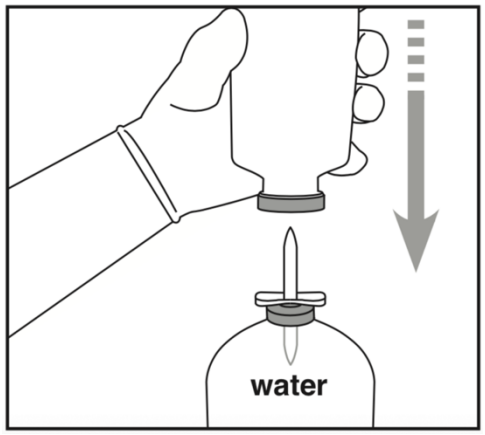
Activase® (alteplase)
Also Required
(not included in kit)
1 Luer Syringe for removing bolus dose, as needed

1 Luer syringe for removing excess volume, as needed

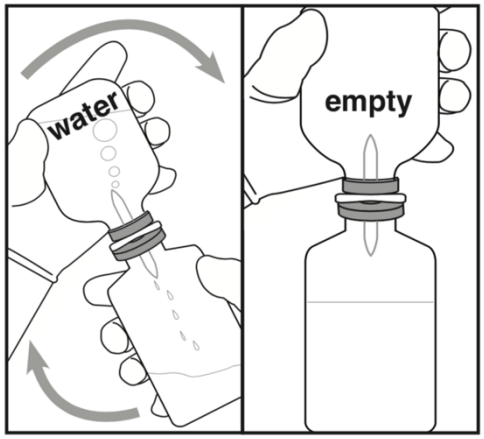
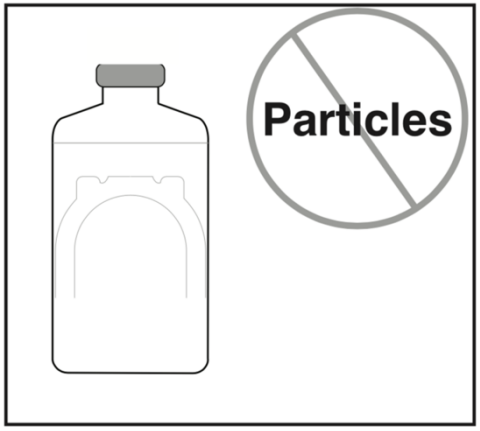
2 large bore needles

2 Alcohol swabs

IV infusion set

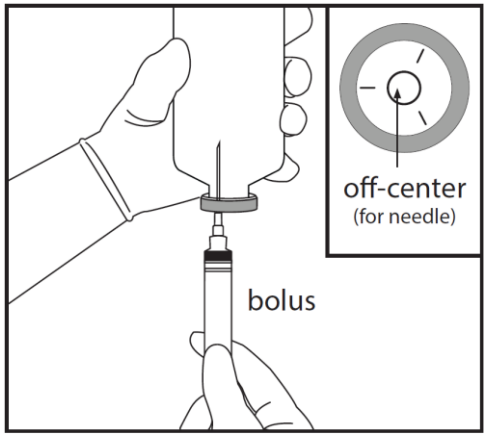
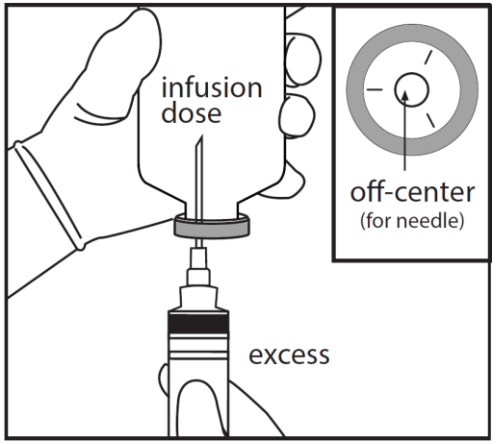
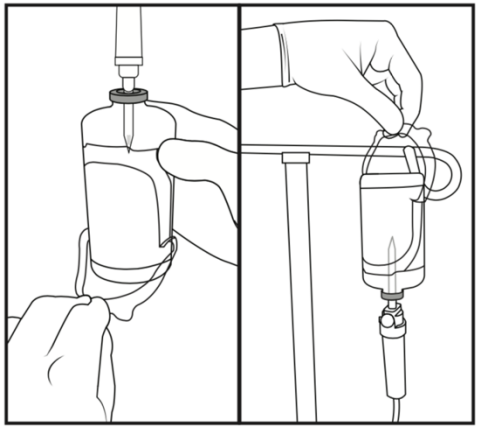


Activase® (alteplase)	**Activase®** (alteplase)	**Activase®** (alteplase)
Reconstitution (use aseptic technique)		
Step 1: Cleaning	**Step 2: Spiking Water vial**	**Step 3: Spiking Activase vial**
		
• Remove caps from both vials. • Wipe both stoppers with alcohol swabs.	• Remove cover from one end of 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. **Do not invert water vial yet. Inverting too early may lead**	• 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. **Inserting the spike off-center could lead to stopper collapse.**

	to leakage and incorrect dosing.	

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 within center ring of stopper, away from hole made by transfer device.
		
		Insert needle 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.

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

• Check if bolus is needed. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw bolus amount. **Do not push any air from syringe into vial (may cause leakage).** • Alternatively, the bolus can be left in the vial and administered via an infusion pump or removed from a port on the infusion line.	• Check if there is excess volume in vial. If yes, attach needle to empty Luer syringe. • Insert needle once through center ring of stopper, away from hole made by transfer device, and slowly withdraw excess volume. **Do not push any air from syringe into vial (may cause leakage).** • Discard any excess volume. • Leave infusion dose in vial.	• 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 clear plastic hanger from vial label. • Hang on IV pole and administer per facility protocol.

Administration Notes
• 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.
Storage & Stability
• 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).