

PRODUCT MONOGRAPH

PrACTIVASE[®] rt-PA

alteplase for injection

Lyophilized Powder for Injection - 50 mg and 100 mg

Fibrinolytic Agent

ACUTE ISCHEMIC STROKE INDICATION ONLY

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Pr **ACTIVASE®** rt-PA

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

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).

INDICATIONS AND CLINICAL USE

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 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.

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, which could result in significant disability or death:

- Symptom onset greater than 3 hours
- Evidence of intracranial hemorrhage on pretreatment evaluation
- Suspicion of subarachnoid hemorrhage on pretreatment evaluation
- Recent intracranial surgery or intraspinal surgery, serious head trauma or previous stroke (within 3 months)
- History of intracranial hemorrhage
- Uncontrolled hypertension at time of treatment (e.g., > 185 mm Hg systolic or >110 mm Hg diastolic)
- Aggressive treatment required to reduce blood pressure to specified limits
- Seizure at the onset of stroke
- Active internal bleeding
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Major surgery within 14 days
- Gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days
- Arterial puncture at a noncompressible site within the previous 7 days
- Blood glucose < 3 or > 22 mmol/L (<50 mg/dL or >400 mg/dL)
- Recent myocardial infarction (<3 months) and/or clinical presentation associated with post-myocardial infarction pericarditis
- Known bleeding diathesis including but not limited to:
 - Current use of oral anticoagulants (e.g., warfarin sodium) or an International Normalized Ratio (INR) > 1.7 or a prothrombin time (PT) > 15 seconds
 - Administration of heparin within 48 hours preceding the onset of stroke and an elevated activated partial thromboplastin time (aPTT) at presentation
 - Platelet count < 100,000/mm³

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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, 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 INDICATIONS AND CLINICAL USE and CONTRAINDICATIONS).

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 Serious Warnings and Precautions).

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 ICH³². **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 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.

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)

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 SYMPTOMS AND TREATMENT OF 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

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

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.

Immune

Angioedema

Angioedema has been observed in post-market experience in patients treated for acute ischemic stroke (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.

Hypersensitivity

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.

Use of Antithrombotics

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.

Hematologic

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.

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.

Nursing Women

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 (age less than 18 years) has not been established. Therefore, treatment of such patients is not recommended.

Geriatrics

The 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.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Bleeding: General

The most frequent adverse reaction associated with ACTIVASE rt-PA (alteplase for injection) is bleeding.^{13,22,23} 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.

Clinical Trial Adverse Drug 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.

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 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-Value²
Total ICH ¹	20 (6.4%)	48 (15.4%)	< 0.01
Symptomatic	4 (1.3%)	25 (8.0%)	< 0.01
Asymptomatic	16 (5.1%)	23 (7.4%)	0.32
Symptomatic ICH within 36 hours	2 (0.6%)	20 (6.4%)	< 0.01
New Ischemic Stroke (3-months)	17 (5.4%)	18 (5.8%)	1.00

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

²Fisher’s Exact Test

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

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

Baseline NIHSS Score	Placebo (n=312)	ACTIVASE rt-PA (n=312)	Odds Ratio and 95% CI
All-cause 90 day mortality	64 (20.5%)	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).

Other 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.

DRUG INTERACTIONS

Overview

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: Hypersensitivity section).

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Blood pressure should be monitored frequently and controlled during and following administration of ACTIVASE rt-PA administration in the management of acute ischemic stroke. In the NINDS t-PA Stroke Trial, blood pressure was actively controlled ($\leq 185/110$ mm Hg) for 24 hours. Blood pressure was monitored during the hospital stay.

The safety and efficacy of this regimen with concomitant administration of heparin and aspirin during the first 24 hours after symptom onset has not been investigated.

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

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.

Preparation and Administration

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

1. By removing the appropriate volume from the vial of reconstituted (1-mg/mL) ACTIVASE rt-PA using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the ACTIVASE rt-PA vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
2. By removing the appropriate volume from a port (second injection site) on the infusion line after the infusion set is primed.

3. By programming an infusion pump to deliver the appropriate volume as a bolus at the initiation of the infusion.

B. The remainder of the ACTIVASE rt-PA dose may be administered as follows:

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

100 mg vial - remove from the vial any quantity of drug in excess of that specified for patient treatment. Insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted ACTIVASE rt-PA. Peel clear plastic hanger from vial label and use loop to hang ACTIVASE rt-PA on IV pole.

Reconstitution and Dilution

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. Because ACTIVASE rt-PA contains no preservatives, it should be reconstituted immediately before use (see STORAGE AND STABILITY).

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

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

Using the transfer device provided, the contents of the accompanying 100 mL vial of Sterile Water for Injection, USP should be added to the contents of the 100 mg vial of ACTIVASE rt-PA powder. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. **NO VACUUM IS PRESENT IN 100 MG VIALS.**

Please refer to the following instructions for Reconstitution and Administration of the 100 mg vials:

1. Use aseptic technique throughout.
2. Remove the protective flip-caps from one vial of ACTIVASE rt-PA and one vial of Sterile Water for Injection, USP [SWFI].
3. Open the package containing the transfer device by peeling the paper label off the package.
4. Remove the protective cap from one end of the transfer device and keeping the vial of SWFI upright, insert the piercing pin vertically into the centre of the stopper of the vial of SWFI.
5. Remove the protective cap from the other end of the transfer device. **DO NOT INVERT THE VIAL OF SWFI.**
6. Holding the vial of ACTIVASE rt-PA upside-down, position it so that the centre of the stopper is directly over the exposed piercing pin of the transfer device.
7. Push the vial of ACTIVASE rt-PA down so that the piercing pin is inserted through the centre of the ACTIVASE rt-PA stopper.
8. Invert the two vials so that the vial of ACTIVASE rt-PA is on the bottom (upright) and the vial of SWFI is upside-down, allowing the SWFI to flow down through the transfer device. Allow the entire contents of the vial of SWFI to flow into the ACTIVASE rt-PA vial (approximately 0.5 mL of SWFI will remain in the diluent vial). Approximately two minutes are required for this procedure.
9. Remove the transfer device and the empty SWFI vial from the ACTIVASE rt-PA vial. Safely discard both the transfer device and the empty diluent vial according to institutional procedures.
10. Swirl gently to dissolve the ACTIVASE rt-PA powder. **DO NOT SHAKE.**

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.

ACTION AND CLINICAL 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.^{3,4} As a result, ACTIVASE rt-PA produces clot dissolution in vivo with minimal systemic effects.^{2,33}

Two controlled trials in acute myocardial infarction (AMI) 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.⁶ 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.⁷

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.⁵

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.¹ 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%.^{6,7} 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%.^{5,7} In contrast, a multicentre trial in AMI patients 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%.⁸

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.¹⁸

Acute Ischemic Stroke Studies

Two placebo-controlled, double-blind trials (The NINDS t-PA Stroke Trial, Part 1 and Part 2) have been conducted in patients with acute ischemic stroke.³¹ Both studies enrolled patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computerized tomography (CT) scan was performed prior to treatment to rule out the presence of intracranial hemorrhage (ICH). Patients were also excluded for the presence of conditions related to risks of bleeding (see CONTRAINDICATIONS), for minor neurological deficit, for rapidly improving symptoms prior to initiating study treatment, or for blood glucose of < 50 or > 400 mg/dL.

Patients were randomized to receive either 0.9 mg/kg ACTIVASE rt-PA (alteplase for injection) (maximum of 90 mg), or placebo. ACTIVASE rt-PA was administered as a 10% initial bolus over 1 minute followed by continuous intravenous infusion of the remainder over 60 minutes (see DOSAGE AND ADMINISTRATION). In patients without recent use of oral anticoagulants or heparin, study treatment was initiated prior to the availability of coagulation study results. However, the infusion was discontinued if either a pre-treatment prothrombin time (PT) > 15 seconds or an elevated activated partial thromboplastin time (aPTT) was identified. Although patients with or without prior acetylsalicylic acid (ASA) use were enrolled, administration of anticoagulants and antiplatelet agents was prohibited for the first 24 hours following symptom onset.

The initial study (NINDS-Part 1, n = 291) evaluated neurological improvement at 24 hours after stroke onset. The primary endpoint, the proportion of patients with a 4 or more point improvement in the National Institutes of Health Stroke Scale (NIHSS) score or complete recovery (NIHSS score = 0), was not significantly different between treatment groups. A secondary analysis suggested improved 3-month outcome associated with ACTIVASE rt-PA treatment using the following stroke assessment scales: Barthel Index, Modified Rankin Scale, Glasgow Outcome Scale, and the NIHSS.

A second study (NINDS-Part 2, n = 333) assessed clinical outcome at 3 months as the primary outcome. A favourable outcome was defined as minimal or no disability using the four stroke assessment scales: Barthel Index (score \geq 95), Modified Rankin Scale (score > 1), Glasgow Outcome Scale (score = 1), and NIHSS (score \leq 1). The results comparing ACTIVASE rt-PA and placebo-treated patients for the four outcome scales together (Generalized Estimating Equations) and individually are presented in Table 3 (for safety data refer to ADVERSE REACTIONS). In this study, depending upon the scale, the favourable outcome of minimal or no disability occurred in at least 11 per 100 more patients treated with ACTIVASE rt-PA than those receiving placebo. Secondary analyses demonstrated consistent functional and neurological improvement within all four stroke scales as indicated by median scores. These results were highly consistent with the 3-month outcome treatment effects observed in the Part 1 study.

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

Analysis	Frequency of Favourable Outcome ¹				p-Value ³
	Placebo (n=165)	ACTIVASE rt-PA (n=168)	Absolute Difference (95% CI)	Relative Frequency ² (95% CI)	
Generalized Estimating Equations (Multivariate)	-	-	-	1.34 (1.05, 1.72)	0.02
Barthel Index	37.6%	50.0%	12.4% (3.0, 21.9)	1.33 (1.04, 1.71)	0.02
Modified Rankin Scale	26.1%	38.7%	12.6% (3.7, 21.6)	1.48 (1.08, 2.04)	0.02
Glasgow Outcome Scale	31.5%	44.0%	12.5% (3.3, 21.8)	1.40 (1.05, 1.85)	0.02
NIHSS	20.0%	31.0%	11.0% (2.6, 19.3)	1.55 (1.06, 2.26)	0.02

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

² Value > 1 indicates frequency of recovery in favour of ACTIVASE rt-PA treatment.

³ p-Value for Relative Frequency is from Generalized Estimating Equations with log link.

The potential treatment effect modifier of efficacy “prior acetylsalicylic acid use” for the combined (parts 1 & 2) study population (placebo n=312; 73 “prior acetylsalicylic acid use” and ACTIVASE rt-PA n=312; 102 “prior acetylsalicylic acid use”) was statistically examined. No clear evidence of treatment effect modification was identified by “prior acetylsalicylic acid use”.

Exploratory, multivariate analyses of both studies combined (n = 624) to investigate potential predictors of ICH and treatment effect modifiers were performed. In ACTIVASE rt-PA treated patients presenting with severe neurological deficit (e.g., NIHSS > 22) or of advanced age (e.g., > 77 years of age), the trends toward increased risk for symptomatic ICH within the first 36 hours were more prominent. Similar trends were also seen for total ICH and for all-cause 90-day mortality in these patients. When risk was assessed by the combination of death and severe disability in these patients, there was no difference between placebo and ACTIVASE rt-PA

groups. Analyses for efficacy suggested a reduced but still favourable clinical outcome for ACTIVASE rt-PA treated patients with severe neurological deficit or advanced age at presentation.

STORAGE AND STABILITY

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.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

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.^{1,2,3,4} Following administration of ACTIVASE rt-PA, there is a decrease (20-30%) in circulating fibrinogen.^{5,6,7,8,9} Decreases in plasminogen and α 2-antiplasmin are also evident.

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.

CLINICAL TRIALS

NINDS Study Summary

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

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

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

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

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

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

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

1. Patients with severe neurological deficits at presentation (e.g. NIH Stroke Scale > 22). There is an increased risk of intracerebral hemorrhage in these patients (odds ratio 1.8; 95% CI, 1.2-1.9)³⁴
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.³⁴

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

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.

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.

REFERENCES

1. Ludbrook PA. Thrombolytic therapy with t-PA. *Cardiovasc Med* February 1986; 37-44.
2. Shafer KE, Jaffe AS. Thrombolytic therapy: current and potential uses. *Drug Ther* October 1983; 95-117.
3. Hoylaerts M, Rijken DC, Lijnen HR, Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator. *J Biol Chem* 1982; 257(6): 2912-19.
4. Tiefenbrunn AJ, Sobel BE. Tissue-type plasminogen activator (t-PA): an agent with promise for selective thrombolysis. *Int J Cardiol* 1985; 7:82-6.
5. Mueller H, Rao AK, Forman SA et al. Thrombolysis in myocardial infarction (TIMI): comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 1987; 10:479-90.
6. Verstraete M, Bory M, Collen D, Erbel R, Lennane RJ, et al. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. *Lancet* April 13, 1985; 842-7.
7. TIMI Study Group. Thrombolysis in myocardial infarction (TIMI) trial: Phase I findings. *New Eng J Med* 1985; 312: 932-6.
8. Collen D, Bounameaux H, De Cock F, Lijnen H, Verstraete M. Analysis of coagulation and fibrinolysis during intravenous infusion of recombinant human tissue-type plasminogen activator in patients with acute myocardial infarction. *Circulation* 1986, 73: 511-17.
9. Topol EJ, Morris DC, Smalling RW et al. A multicentre randomized placebo controlled trial of a new form of intravenous recombinant tissue type plasminogen activator (Activase®) in acute myocardial infarction. *J Am Coll Card* 1987; 9:1205.
13. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New Eng J Med* 1993; 329: 673-82.
18. Reduto LA, Smalling RW, Freund GC, Gould KL. Intracoronary infusion of streptokinase in patients with acute myocardial infarction: effects of reperfusion on left ventricular performance. *Am J Cardiol* 1981; 48: 403-9.
22. Califf RM, Topol EJ, et al. Haemorrhagic complications associated with the use of intravenous tissue plasminogen activator in treatment of acute myocardial infarction. *Am J Med* 1988, 353-9.

23. Bovill EG, Terrin ML, et al. Haemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. *Ann Int Med* 1991; 115: 256-65.
31. The National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *New Engl J Med.* 1995;333:1581B7.
32. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. For the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;274:1017B25.
33. Lynden PD, Zivin JA, Clark WA, Madden K, Sasse KC, Mazzarella V, Terry RD, Press GA. Tissue plasminogen activator-mediated thrombolysis of cerebral emboli and its effect on hemorrhagic infarction in rabbits. *Neurology* 1989;39:703-708.
34. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997;28:2109-2118
35. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). *Lancet* 1998; 352:1-15.

PART III: CONSUMER INFORMATION

Pr **ACTIVASE®** rt-PA
alteplase for injection

This leaflet is part III of a three-part "Product Monograph" published when ACTIVASE rt-PA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACTIVASE rt-PA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is 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

What it does:

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).

When it should not be used:

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

Treatment of patients with problems with nerve, spinal cord or brain function or with rapidly

improving symptoms is not recommended.

What the medicinal ingredient is:

alteplase

What the important nonmedicinal ingredients are:

L-arginine, phosphoric acid and polysorbate 80

What dosage forms it comes in:

ACTIVASE rt-PA is available in:

1. 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.
2. 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

WARNINGS AND PRECAUTIONS**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.

The most common complication encountered during therapy with ACTIVASE rt-PA (alteplase for injection) is bleeding.

BEFORE ACTIVASE rt-PA is given, your doctor will review the possible risks based on your medical condition and history, including if you are/have/had:

- Severe problems with the nerve, spinal cord or brain function
- Major early infarct signs such as swelling, growing mass, or midline shift (detected through a CT scan)
- Recent major surgery or trauma
- Clinical evidence or history of transient ischemic attacks

- Recent gastrointestinal or urinary tract bleeding
- High blood pressure (i.e., ≥ 175 mm Hg systolic and/or ≥ 110 mm Hg diastolic)
- History or clinical evidence of high blood pressure in a patient over 70 years old
- Over 75 years old
- Problems with the heart or heartbeat
- Severe liver failure
- Pregnancy
- Serious infection or inflammation
- Taking medications that affect blood clotting (i.e., warfarin sodium)
- Use of blood dissolving drugs
- Cholesterol embolization
- Abnormal blood glucose levels

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ACTIVASE rt-PA include:

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

PROPER USE OF THIS MEDICATION

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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
- Internal bleeding, involving the gastrointestinal and urinary tract, lungs, or within the skull
- Potential bleeding sites as a result of recent invasive procedure (i.e., catheter insertions, puncture, surgery)
- Swelling or high pressure in the brain, uncontrollable shaking (seizure), new ischemic stroke, embolism

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.

HOW TO STORE IT

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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.rochecanada.com> or by contacting the sponsor Hoffmann-La Roche Limited, at: 1-888-762-4388

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