



# PRODUCT MONOGRAPH

## **Activase<sup>®</sup> rt-PA** (Alteplase)

Lyophilized Powder for Injection - 50 mg and 100 mg

Fibrinolytic Agent

Product Monograph for  
ACUTE ISCHEMIC STROKE INDICATION ONLY

Distributed by:  
**HOFFMANN-LA ROCHE LIMITED**  
2455 Meadowpine Boulevard  
Mississauga, Ontario L5N 6L7

Manufactured by:  
Genentech, Inc.  
California, U.S.A.

Date of Approval:  
**February 28, 2005**

<sup>®</sup> Registered Trade Mark of Genentech, Inc.  
Used under license by Hoffmann-La Roche Limited

Control #: 075039

## PRODUCT MONOGRAPH

### Activase® rt-PA (alteplase)

Lyophilized Powder for Injection - 50 mg and 100 mg

#### FIBRINOLYTIC AGENT

CAUTION: ACTIVASE is a drug known to cause severe bleeding and an increased incidence of intracranial hemorrhage. Use of ACTIVASE 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).

Based on burden of evidence, treatment of patients with acute ischemic stroke more than three hours after symptom onset is not recommended (see CONTRAINDICATIONS).

#### ACTIONS AND CLINICAL PHARMACOLOGY

##### ACUTE ISCHEMIC STROKE

ACTIVASE(alteplase) is a serine protease which has the property of fibrin-enhanced conversion of plasminogen to plasmin. ACTIVASE produces minimal conversion of plasminogen in the absence of fibrin; and when introduced into the systemic circulation, ACTIVASE binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with minimal systemic effects.<sup>1,2,3,4</sup> Following administration of ACTIVASE, there is a decrease (20-30%) in circulating fibrinogen.<sup>5,6,7,8,9</sup> Decreases in plasminogen and  $\alpha$ 2-antiplasmin are also evident.

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

#### INDICATIONS AND CLINICAL USE

##### MANAGEMENT OF ACUTE ISCHEMIC STROKE

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

ACTIVASE (alteplase) is indicated for the management of acute ischemic stroke in adults for improving neurological recovery and reducing the incidence of disability. Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of hemorrhage. Eligibility criteria of the 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 for this indication.

**NINDS STUDY SUMMARY**

The National Institute of Neurological Disorders and Stroke (NINDS) acute ischemic stroke study<sup>31</sup> 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 1).

**Table 1**  
**The NINDS t-PA Stroke Trial, Part 2**  
 3-Month Efficacy Outcomes

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

<sup>1</sup>Favorable 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 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)<sup>34</sup>
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.<sup>34</sup>

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

### **CASES Study Summary**

The Canadian ACTIVASE 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 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.

---

## CONTRAINDICATIONS

### ACUTE ISCHEMIC STROKE

ACTIVASE(alteplase) 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<sup>3</sup>

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

## WARNINGS

### ACUTE ISCHEMIC STROKE

**ACTIVASE is a drug known to cause severe bleeding and an increased incidence of intracranial hemorrhage. Use of ACTIVASE for the treatment of stroke is limited to physicians experienced in acute stroke management (see boxed CAUTION).**

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<sup>32</sup>. **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 (alteplase) 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 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.

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.

**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 for the management of acute ischemic stroke is unknown.

**OROLINGUAL ANGIOEDEMA**

Orolingual angioedema has been observed in post-market experience in patients treated for acute ischemic stroke and in patients treated for acute myocardial infarction (see PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Allergic Reactions).

Onset of angioedema occurred during and up to 2 hours after infusion of ACTIVASE. In many cases, patients were receiving concomitant Angiotensin-converting enzyme inhibitors. Patients treated with ACTIVASE should be monitored during and for several hours after infusion for signs of orolingual angioedema. If angioedema is noted, promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids or epinephrine) and consider discontinuing the ACTIVASE infusion. Rare fatal cases of hemorrhage associated with traumatic intubation in patients administered ACTIVASE have been reported.

**WARNINGS: GENERAL****BLEEDING**

The most common complication encountered during therapy with ACTIVASE (alteplase) 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 and bleeding from recent puncture sites may occur. Therefore, therapy with ACTIVASE, 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. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE, 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 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 therapy for both approved indications 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 noncompressible 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;
- High likelihood or known presence of left heart thrombus, e.g. mitral stenosis with atrial fibrillation; apical MI, with thrombus;
- 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.

### **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.

---

## PRECAUTIONS

### ACUTE ISCHEMIC STROKE

ACTIVASE (alteplase) 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 and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

### DRUG INTERACTIONS

The interaction of ACTIVASE with other drugs has not been studied. In addition to bleeding associated with 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 infusion.

Orolingual angioedema has been observed after ACTIVASE administration in patients receiving concomitant ACE inhibitor therapy. However, the significance of this observation has not been determined (see ADVERSE REACTIONS: Allergic Reactions section).

### LABORATORY TESTS

During ACTIVASE 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 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.

### USE IN THE ELDERLY

The risks of therapy may be increased in the elderly (see **WARNINGS**).

In ACTIVASE treated patients (NINDS study) of advanced age (eg. >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.

### USE IN CHILDREN

Safety and effectiveness of ACTIVASE in children (age less than 18 years) has not been established. Therefore treatment of such patients is not recommended.

### USE IN PREGNANCY

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.

**NURSING MOTHERS**

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

**READMINISTRATION**

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

**ADVERSE REACTIONS****ACUTE ISCHEMIC STROKE**

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

The incidences of ICH, and new ischemic stroke following ACTIVASE treatment compared to placebo are presented in Table 2 as a combined safety analysis (n = 624) for Parts 1 and 2. These data indicated a significant increase in ICH following ACTIVASE 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 treated patients ( $p < 0.01$ ). Potential predictors of symptomatic ICH within 36 hours of study drug administration were baseline values of NIHSS score, fibrinogen ( $< 200 \text{ mg/dL}$ ), and platelet count ( $< 150,000/\text{uL}$ ). These predictors were the same in both treatment groups.

**Table 2**  
**The NINDS t-PA Stroke Trial**  
**Safety Outcome**

	Part 1 and Part 2 Combined		
	Placebo (n = 312)	ACTIVASE (n = 312)	p-Value <sup>2</sup>
Total ICH <sup>1</sup>	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

<sup>1</sup>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.

<sup>2</sup>Fisher's Exact Test

Table 3 displays the incidences of all-cause 90 day mortality and mortality rates and odds ratios by baseline NIHSS subgroup. In ACTIVASE 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 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 3**  
All-cause 90-Day Mortality for Baseline NIHSS Subgroups

Baseline NIHSS Score	Placebo (n=312)	ACTIVASE (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) <sup>a</sup>
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 patients. (Where 95% CIs include 1, difference is non-significant on this sample size).

<sup>a</sup> Significant difference (p<0.05).

### BLEEDING: GENERAL

The most frequent adverse reaction associated with ACTIVASE (alteplase) is bleeding.<sup>13,22,23</sup> 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 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. 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 treated patients compared to 3.8% for placebo (p = 0.19, using Mantel-Haenszel Chi-Square).

### ALLERGIC REACTIONS

Allergic-type reactions, e.g. anaphylactoid reaction, laryngeal edema, rash, urticaria and orolingual angioedema (see WARNINGS) have been reported. A cause and effect relationship has not been established. When such reactions occur they usually respond to conventional therapy.

## OTHER 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.

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

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

### ACUTE ISCHEMIC STROKE

Overdosage could lead to serious bleeding. Should serious bleeding occur in a critical location, the infusion of ACTIVASE (alteplase) 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.

## DOSAGE AND ADMINISTRATION

### ACUTE ISCHEMIC STROKE

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

**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.

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

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 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 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 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. Hang the ACTIVASE vial from the plastic molded capping attached to the bottom of the vial.

### RECONSTITUTION AND DILUTION

ACTIVASE should be reconstituted by aseptically adding to the vial of ACTIVASE, 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 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 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 contains no preservatives, it should be reconstituted immediately before use (see Stability and Storage).

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 solution. Solutions should be administered as described above. Unused infusion solution should be immediately discarded.**

**50 mg vials:** Using 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 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 accompanying 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 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 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 down so that the piercing pin is inserted through the centre of the ACTIVASE stopper.
  8. Invert the two vials so that the vial of ACTIVASE is on the bottom (upright) and the vial of SWFI is upside-down, allowing the SWFI to flow down through the transfer device. Allow the entire contents of the vial of SWFI to flow into the ACTIVASE vial (approximately 0.5 mL of SWFI will remain in the diluent vial). Approximately two minutes are required for this procedure.
  9. Remove the transfer device and the empty SWFI vial from the ACTIVASE vial. Safely discard both the transfer device and the empty diluent vial according to institutional procedures.
  10. Swirl gently to dissolve the ACTIVASE powder. DO NOT SHAKE.

---

## PHARMACEUTICAL INFORMATION

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

The quantitative composition of the lyophilized product is:

<u>50 mg (29 x 10<sup>6</sup> I.U.) Vial</u>	<u>100 mg (58 x 10<sup>6</sup> I.U.) Vial</u>
Alteplase 50 mg	Alteplase 100 mg
L-Arginine 1.7 g	L-Arginine 3.5 g
Phosphoric Acid 0.5 g	Phosphoric Acid 1.0 g
Polysorbate 80, less than or equal to 4 mg	Polysorbate 80, less than or equal to 11 mg
Vacuum present	No Vacuum present

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 x 10<sup>4</sup> I.U./mg ACTIVASE).

### STABILITY AND STORAGE

Lyophilized ACTIVASE 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 (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.

## AVAILABILITY OF DOSAGE FORMS

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

ACTIVASE is available in:

1. Boxes each containing one (1) vial of ACTIVASE 50 mg and one (1) vial of Sterile Water for Injection, USP 50 mL, for preparing a sterile solution of ACTIVASE.
2. Boxes each containing one (1) vial of ACTIVASE 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.

## PHARMACOLOGY

### EFFECT ON COAGULATION

ACTIVASE(alteplase) differs from other plasminogen activators in that it is fibrin dependent. Relatively selective fibrinolysis with ACTIVASE, 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.<sup>3,4</sup> As a result, ACTIVASE produces clot dissolution in vivo with minimal systemic effects.<sup>2,33</sup>

Two controlled trials in acute myocardial infarction (AMI) patients have measured circulating plasma fibrinogen levels after infusion of activators. Results with ACTIVASE 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 treated patients compared with approximately 12% for those treated with streptokinase.<sup>6</sup> In the second study, post-treatment levels of fibrinogen (measured by the sodium phosphate precipitation method) were approximately 75% of baseline with ACTIVASE compared with 53% with streptokinase.<sup>7</sup>

In a dose response trial conducted by the National Heart, Lung and Blood Institute (NHLBI), comparing three different doses of ACTIVASE 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.<sup>5</sup>

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.<sup>1</sup> In two multicentre trials of ACTIVASE 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%.<sup>6,7</sup> In two multicentre trials of ACTIVASE in AMI patients, the incidence of fibrinogen levels below 100 mg% (measured with clotting rate techniques) was less than 25%.<sup>5,7</sup> In contrast, a multicentre trial in AMI patients comparing ACTIVASE to streptokinase found the incidence of fibrinogen levels below 100 mg% in the streptokinase group (measured with clotting rate techniques) to be 95%.<sup>8</sup>

Another measure of systemic fibrinolytic activation is the elevation of fibrinogen-fibrin degradation products (FDP's). In a study in AMI patients comparing ACTIVASE to streptokinase, FDP's increased to 0.75 mg/mL in the streptokinase group but to only 0.10 mg/mL in the ACTIVASE group.<sup>18</sup>

### 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.<sup>31</sup> 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 (alteplase) (maximum of 90 mg), or placebo. ACTIVASE 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 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 favorable outcome was defined as minimal or no disability using the four stroke assessment scales: Barthel Index (score ≥ 95), Modified Rankin Scale (score > 1), Glasgow Outcome Scale (score = 1), and NIHSS (score ≤ 1). The results comparing ACTIVASE and placebo-treated patients for the four outcome scales together (Generalized Estimating Equations) and individually are presented in Table 4 (for safety data refer to ADVERSE REACTIONS). In this study, depending upon the scale, the favorable outcome of minimal or no disability occurred in at least 11 per 100 more patients treated with ACTIVASE 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 4**  
**The NINDS t-PA Stroke Trial, Part 2**  
**3-Month Efficacy Outcomes**

Analysis	Frequency of Favorable Outcome <sup>1</sup>				p-Value <sup>3</sup>
	Placebo (n=165)	ACTIVASE (n=168)	Absolute Difference (95% CI)	Relative Frequency <sup>2</sup> (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

<sup>1</sup>Favorable Outcome is defined as recovery with minimal or no disability.

<sup>2</sup>Value > 1 indicates frequency of recovery in favor of ACTIVASE treatment.

<sup>3</sup>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 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 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 groups. Analyses for efficacy suggested a reduced but still favorable clinical outcome for ACTIVASE treated patients with severe neurological deficit or advanced age at presentation.

## 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.

### SUBACUTE 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 TOXICOLOGY**

Acute and subacute 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.