Indication
Activase® (alteplase) is indicated for the treatment of acute ischemic stroke. Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment. Initiate treatment as soon as possible but within 3 hours after symptom onset.

Important Safety Information
Contraindications
Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit: current intracranial hemorrhage (ICH); subarachnoid hemorrhage; active internal bleeding; recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms); bleeding diathesis; and current severe uncontrolled hypertension.

Please see select Important Safety Information throughout and the full Prescribing Information below.
Clinical presentation of acute ischemic stroke (AIS)

Common symptoms of anterior stroke include*¹:

- Aphasia
- Disturbed consciousness
- Dysarthria
- Facial palsy
- Hemisensory deficits
- Homolateral motor deficit

Common symptoms of posterior stroke include*²:

- Diplopia
- Dizziness
- Dysarthria
- Dysphagia
- Dystaxia

*The symptoms listed for anterior and posterior strokes are not exhaustive, nor are they mutually exclusive. Symptoms alone are not sufficient to diagnose the location of the occlusion, which should be confirmed using brain imaging.¹
Conditions that may mimic stroke³

- Bell’s palsy
- Complicated migraine
- Conversion disorder/psychogenic conditions
- Hypertensive encephalopathy
- Hypoglycemia
- Infection/abscess
- Seizures
- Tumor
EMS management of patients with suspected stroke$^3,4$

**On scene**

- Manage CABs (chest compressions-airway-breathing)—give ventilatory assistance, if needed
- Perform prehospital stroke assessment
- Establish and record exact time when the patient was last seen normal, as opposed to when the patient was found with neurological deficits
- Obtain the name of a family contact and their phone number
- Ascertain the patient’s medical history, including relevant surgeries, medications, and allergies; particular attention should be paid to potential stroke risk factors, such as hypertension, diabetes, previous strokes, recent surgeries, and smoking

**In transit**

- Rapid transport to the closest IV alteplase–capable hospital,* which may involve air medical transport or bypass of hospitals without IV alteplase capabilities
- Notify the receiving hospital that a patient with suspected stroke is en route
- Check and record blood glucose to assess for hypoglycemia
- Establish cardiac monitoring and IV access, if possible

*If no such centers exist, patient should be brought to the most appropriate institution that provides emergency stroke care.

EMS=emergency medical services; IV=intravenous.
Prehospital stroke assessments

Recommendation from the AHA/ASA 2018 Guideline

Ensure that patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized instrument for stroke screening, such as the Face, Arm, Speech Test (FAST) scale, Los Angeles Prehospital Stroke Screen (LAPSS), or Cincinnati Prehospital Stroke Scale (CPSS) (Class I; Level of Evidence B-NR).

Examples of other prehospital stroke assessments include the Los Angeles Motor Scale (LAMS), the Rapid Arterial Occlusion Evaluation (RACE) scale, and the Vision, Aphasia, and Neglect (VAN) screening tool.

AHA/ASA=American Heart Association/American Stroke Association; Class I=procedure is considered effective (strong strength; benefit is greater than risk); Level of Evidence B-NR=data from 1 or more nonrandomized studies or meta-analyses of such studies.
1a. Level of Consciousness (LOC)

0 = Alert; keenly responsive
1 = Not alert, but arousable by minor stimulation
2 = Not alert; requires repeated stimulation to attend or is obtunded and requires strong or painful stimulation to make movements
3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic

The investigator must choose a response if full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages, etc. A score of 3 is given only if the patient makes no movement (other than reflexive posturing) in response to noxious stimuli.

1b. LOC Questions

Ask the patient: “What month is it?” “How old are you?”

0 = Answers both questions correctly
1 = Answers 1 question correctly
2 = Answers neither question correctly

Score only the initial answer (there is no credit for being close). Patients unable to speak due to intubation, orotracheal trauma, severe dysarthria, language barrier, etc, are scored 1. Aphasic and stuporous patients are scored 2.
**1c. LOC Commands**

Ask the patient to: “Open and close your eyes.” “Grip and release your hand.”

- **0** = Performs both tasks correctly
- **1** = Performs 1 task correctly
- **2** = Performs neither task correctly

Substitute another 1-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to the command, the task should be demonstrated to him or her (pantomime) and the results scored (ie, follows none, 1, or 2 commands). Patients with trauma, amputation, or other physical impediments should be given suitable 1-step commands. Only the first attempt is scored.

**2. Best Gaze (only horizontal movement tested)**

Establish eye contact and ask the patient to: “Follow my finger.”

- **0** = Normal
- **1** = Partial gaze palsy
- **2** = Forced deviation or total gaze paresis is not overcome by oculocephalic maneuver

Appropriate for aphasic patients. Score voluntary or reflexive horizontal eye movements (do not perform caloric test). Test patients with ocular trauma, bandages, preexisting blindness, etc, for reflexive movement and a choice made by the investigator. Patients with conjugate deviation of the eyes (overcome by voluntary or reflexive activity) and those with isolated peripheral nerve paresis (cranial nerve III, IV, or VI) are scored 1.
3. **Visual Fields**

Use confrontation, finger counting, or visual threat. Confront upper/lower quadrants of visual field.

- 0 = No visual loss
- 1 = Partial hemianopsia
- 2 = Complete hemianopsia
- 3 = Bilateral hemianopsia

Test patients with unilateral blindness or enucleation in remaining eye. Patients with clear-cut asymmetry, including quadrantanopia, are scored 1. Blind patients are scored 3. Test again using double simultaneous stimulation. Score 1 for extinction and record under item 11.

4. **Facial Palsy**

Through words or pantomime, encourage the patient to:

- “Show me your teeth.”
- “Raise your eyebrows.”
- “Close your eyes.”

- 0 = Normal symmetrical movements
- 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
- 2 = Partial paralysis (total or near-total paralysis of lower face)
- 3 = Complete paralysis of one or both sides

If possible, remove facial bandages, orotracheal tube, tape, etc, before testing. In poorly responsive patients, score symmetry of grimace in response to noxious stimuli.
5. Motor Arm

Alternately position the patient's arms. Extend each arm with palms down (90 degrees if sitting, 45 degrees if supine).

0 = No drift
1 = Drift
2 = Some effort vs gravity
3 = No effort vs gravity
4 = No movement
UN = Amputation or joint fusion

Test each arm in turn (nonparetic arm first). Drift is scored if arm falls before 10 seconds. Score untestable (UN) only for patients with amputations or joint fusions of the shoulder.

6. Motor Leg

Alternately position the patient's legs. Extend each leg (30 degrees, always while supine).

0 = No drift
1 = Drift
2 = Some effort vs gravity
3 = No effort vs gravity
4 = No movement
UN = Amputation or joint fusion

Test each leg in turn (nonparetic leg first). Drift is scored if leg falls before 5 seconds. Score UN only for patients with amputations or joint fusions of the hip.
7. **Limb Ataxia**

Ask patient (eyes open) to: “Touch your finger to your nose.”
“Touch your heel to your shin.”

0 = Absent

1 = Present in 1 limb

2 = Present in 2 limbs

**UN** = Amputation or joint fusion

Perform finger-nose-finger and heel-shin tests on both sides to determine unilateral cerebellar lesion. Score 0 for patients who are paralyzed or cannot understand the commands. Score 1 or 2 only if ataxia is disproportionate to weakness. Score UN only for patients with amputation or joint fusions.

8. **Sensory**

Test as many body parts as possible (arms [not hands], legs, trunk, face) for sensation using pinprick or noxious stimulus (in the obtunded or aphasic patient).

0 = Normal

1 = Mild-to-moderate sensory loss

2 = Severe to total sensory loss

Score sensory loss due to stroke only. Stuporous and aphasic patients are scored 0 or 1. Patients with brain-stem stroke and bilateral sensory loss, quadriplegic patients who do not respond, and comatose patients (item 1a = 3) are scored 2. A score of 2 is only given when severe or total loss of sensation is clearly demonstrated.
9. Best Language

Using pictures and a sentence list (see following cards), ask the patient to:
“Describe what you see in this picture.” “Name the items in this picture.”
“Read these sentences.”

0  = No aphasia
1  = Mild-to-moderate aphasia
2  = Severe aphasia
3  = Mute, global aphasia

Patients with visual loss can be asked to identify and describe objects placed in their hand. Intubated patients should be asked to write their answers. The examiner must choose a score for stuporous or uncooperative patients. Comatose patients (item 1a = 3) are scored 3. A score of 3 is only given if the patient is mute and unable to follow 1-step commands.
NIHSS testing card—picture description

(NIHSS information on pages 6-17)

NIHSS testing card—naming list

(NIHSS information on pages 6-17)

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.
10. **Dysarthria**

Using a simple word list (see next card), ask the patient to:
“Read these words.” “Repeat these words.”

**0** = Normal articulation

**1** = Mild-to-moderate dysarthria

**2** = Severe dysarthria

**UN** = Intubated or other physical barrier

Patients with severe aphasia can be scored based on the clarity of articulation of their spontaneous speech. Score UN only for patients who are intubated or have other physical barriers to speech. Do not tell patients why they are being tested.
MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER
11. Extinction and Inattention

Sufficient information to determine these scores may have been obtained during the prior testing.

0 = No abnormality

1 = Visual, tactile, auditory, spatial, or personal inattention

2 = Profound hemi-inattention or extinction to more than 1 modality

Lack of patient response and inattention may already be evident from the previous items. Score 0 if the patient has a severe visual loss preventing visual double simultaneous stimulation but the response to cutaneous stimuli is normal, or if the patient has aphasia but does appear to attend to both sides. The presence of visual or spatial neglect or anosognosia may also be evidence of abnormality.
Studies indicate that the NIHSS scores lesion-specific deficits unevenly; for example:

- The NIHSS scoring system is heavily biased toward anterior circulation and left-hemisphere strokes\(^9\)
- Cranial nerve signs and ataxia, typical of posterior circulation strokes, receive fewer points or are excluded entirely\(^10\)
- Right-hemisphere strokes are often underestimated, as only 2 points are directed toward neglect, compared to 7 toward language\(^11\)

Due to this uneven scoring, it is therefore possible that, depending on the location of the infarct, some patients may have a low NIHSS score but still have persistent neurological deficits.\(^9\)
Differentiate between disabling and nondisabling deficits

For each patient, all neurological deficits present at the time of the treatment decision should be considered in the context of individual risk and benefit, as well as the patient’s baseline functional status.¹⁴

Activase® (alteplase) clinical trials enrolled patients with a measurable neurological deficit, defined as impairment of language, motor function, cognition, gaze, vision, or neglect.¹²,¹³

**Deficits considered by the AHA/ASA to be disabling¹²:**
- Complete hemianopsia (≥2 on NIHSS question 3)
- Severe aphasia (≥2 on NIHSS question 9)
- Visual or sensory extinction (≥1 on NIHSS question 11)
- Any weakness limiting sustained effort against gravity (≥2 on NIHSS question 5 or 6)
- Any deficits that lead to a total NIHSS score >5
- Any remaining deficit the patient or practitioner considers potentially disabling (clinical judgment is required)
Determine if your patients’ deficits are disabling

Consider asking your patients the following questions:

- Will you be able to return to work as normal?
- Will you be able to perform your everyday activities and hobbies?
- Do you consider any of your symptoms to be disabling? (For example, in patients with hand weakness: “Will weakness of your hand affect your daily life?”)

Consider the following questions about your patients:

- Can they sit on the edge of the bed? Are they ambulatory?
- Are they able to hold a conversation?
Quantify the level of disability

Measurement of a patient's ability to perform activities of daily living, including instrumental activities, should be a treatment consideration. The modified Rankin Scale measures the ability of a patient to function independently without assistance.

**Modified Rankin Scale**:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
AHA/ASA 2018 Guideline: Immediate diagnostic tests for all patients with suspected AIS

- Brain imaging by noncontrast computed tomography (CT) or magnetic resonance imaging (MRI)
- Blood glucose
- Blood pressure
- Oxygen saturation
- Platelet count*
- Troponin assessment*
- Prothombin time (PT)/international normalized ratio (INR)*
- Activated partial thromboplastin time (aPTT)*
- Electrocardiogram*

*Although it is desirable to know the results of these tests before administering alteplase, fibrinolytic therapy should not be delayed while awaiting results unless: 1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, 2) the patient has received heparin or warfarin, or 3) the patient has received other anticoagulants (direct thrombin inhibitors or direct factor Xa inhibitors).
Recommendations from AHA/ASA 2018 Guideline

- Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after AIS is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia (Class IIa; Level of Evidence C-LD)

- Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS (Class I; Level of Evidence C-LD)
Recommendations from AHA/ASA 2018 Guideline
If patients are otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg, administer:

- Labetalol 10-20 mg IV over 1-2 minutes, may repeat 1 time; or
- Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5-15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
- Clevidipine 1-2 mg/h IV, titrate by doubling the dose every 2-5 min until desired BP reached, maximum 21 mg/h; or
- Other agents (eg, hydralazine, enalaprilat) may also be considered

If BP is not maintained ≤185/110 mm Hg, do not administer alteplase.
BP management in patients with AIS

• In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (eg, concomitant acute coronary event, acute heart failure, aortic dissection, postthrombolysis symptomatic intracranial hemorrhage, or preeclampsia/eclampsia). Lowering BP initially by 15% is probably safe (Class I; Level of Evidence C-EO)

• In patients with BP ≥220/120 mm Hg who did not receive IV alteplase or endovascular therapy and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke (Class IIb; Level of Evidence C-EO)

Level C-EO=consensus of expert opinion based on clinical experience.

Please see select Important Safety Information throughout and the full Prescribing Information below.
AHA/ASA 2018 Guideline recommends IV alteplase use for management of AIS

IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state (Class I; Level of Evidence A).

In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible (Class I; Level of Evidence A).

Level of Evidence A=data derived from multiple randomized clinical trials or meta-analyses.
Activase® (alteplase) is also recommended for patients prior to mechanical thrombectomy

AHA/ASA 2018 Guideline

Patients eligible for IV alteplase should receive IV alteplase even if endovascular therapies are being considered (Class I; Level of Evidence A).

SVIN 2015 Recommendations

Endovascular mechanical thrombectomy, in addition to treatment with IV rtPA in eligible patients, is recommended for anterior circulation LVO ischemic strokes in patients presenting within 6 hours after symptom onset (Class I; Level of Evidence A).

LVO=large vessel occlusion; rtPA=recombinant tissue plasminogen activator; SVIN=Society of Vascular and Interventional Neurology.

Please see select Important Safety Information throughout and the full Prescribing Information below.
Since 2015, the Joint Commission has required DTN of ≤60 minutes in 50% of all eligible AIS patients receiving Activase® (alteplase)\textsuperscript{17}

Target: Stroke has established a more aggressive goal\textsuperscript{18}:

- DTN within 60 minutes in at least 75% of patients
- DTN within 45 minutes in at least 50% of patients

\[\begin{array}{c}
\text{DTN} \leq 60 \text{ minutes}\textsuperscript{18} \\
0 \text{ min} \leq 10 \text{ min} \leq 15 \text{ min} \leq 25 \text{ min} \leq 45 \text{ min} \leq 60 \text{ min}
\end{array}\]

\[\begin{array}{c}
\text{DTN} \leq 45 \text{ minutes}\textsuperscript{18} \\
0 \text{ min} \leq 20 \text{ min} \leq 35 \text{ min} \leq 45 \text{ min}
\end{array}\]

*Initiate treatment with Activase as soon as possible but within 3 hours after symptom onset.\textsuperscript{13}

ED=emergency department; NIH=National Institutes of Health.
Patient selection for Activase therapy\textsuperscript{13}

- Activase is indicated for the treatment of AIS
- Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment
- Initiate treatment as soon as possible but within 3 hours after symptom onset

Please see select Important Safety Information throughout and the full Prescribing Information below.
Contraindications to Activase® (alteplase) therapy

Do not administer Activase to treat AIS in the following situations in which the risk of bleeding is greater than the potential benefit:

- Current intracranial hemorrhage
- Subarachnoid hemorrhage
- Active internal bleeding
- Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
- Presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms)
- Bleeding diathesis*
- Current severe uncontrolled hypertension

*The 2018 AHA/ASA Guideline advises against treatment with IV alteplase in patients4:
  - With a platelet count <100,000/mm³, INR >1.7, aPTT >40 seconds, or PT >15 seconds
  - Who have a history of warfarin use and an INR >1.7 and/or a PT >15 seconds

- Who have received a treatment dose of low-molecular-weight heparin within the previous 24 hours
- Who are taking direct thrombin inhibitors or direct factor Xa inhibitors, unless the laboratory tests are normal or the patient has not received a dose of these agents for >48 hours
FDA-approved dosing of Activase for AIS\textsuperscript{13}

- The recommended dose of Activase is 0.9 mg/kg (not to exceed 90-mg total dose) infused intravenously over 60 minutes with 10% of the total dose administered as an initial bolus over 1 minute.

FDA=Food and Drug Administration.

Please see select Important Safety Information throughout and the full Prescribing Information below.
Recommendations from AHA/ASA 2018 Guideline⁴
To maintain BP ≤180/105 mm Hg, monitor BP:
• Every 15 minutes for 2 hours from the start of alteplase therapy;
• Then every 30 minutes for 6 hours; and
• Then every hour for 16 hours

If systolic BP is >180-230 mm Hg or diastolic BP is >105-120 mm Hg, administer:
• Labetalol 10 mg IV followed by continuous IV infusion 2-8 mg/min; or
• Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5-15 minutes (maximum 15 mg/h); or
• Clevidipine 1-2 mg/h IV, titrate by doubling the dose every 2-5 min until desired BP reached (maximum 21 mg/h)

If BP is not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside.
Monitor BP every 15 minutes during the 1-hour infusion$^{4,13}$
- Once IV alteplase is given, the BP must be maintained at or below 180/105 mm Hg to limit the risk of intracranial hemorrhage
- Administer antihypertensive medications to maintain BP at or below these levels

Perform neurological assessments$^4$
The use of a stroke rating scale, preferably the NIHSS, is recommended.
- Repeat every 15 minutes during the 1-hour infusion to monitor for neurological deterioration

Please see select Important Safety Information throughout and the full Prescribing Information below.
Check for major and/or minor bleeding
All body secretions should be tested for occult blood.\textsuperscript{19}

- Major bleeding: intracranial, retroperitoneal, gastrointestinal, or genitourinary hemorrhages\textsuperscript{20}
- Minor bleeding: gums, venipuncture sites, hematuria, hemoptyisis, skin hematomas, or ecchymosis\textsuperscript{20}
- Arterial and venous punctures should be minimized and checked frequently\textsuperscript{13,19}

Discontinue infusion and obtain an emergency CT scan if the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination.\textsuperscript{4}

Monitor for signs of hypersensitivity\textsuperscript{13}
If signs of hypersensitivity occur, such as an anaphylactoid reaction or development of angioedema, discontinue the Activase infusion and promptly institute appropriate therapy.

Please see select Important Safety Information throughout and the full Prescribing Information below.
Patient monitoring post-Activase administration

Continue to monitor for neurological deterioration
• Every 15 minutes for the first hour after the infusion is stopped
• Every 30 minutes for the next 6 hours
• Hourly from the eighth postinfusion hour until 24 hours after the infusion is stopped

Continue to check for major and/or minor bleeding

Continue to monitor and control BP
• Every 15 minutes for the first hour after the infusion is stopped
• Every 30 minutes for the next 6 hours
• Hourly from the eighth postinfusion hour until 24 hours after the infusion is stopped

Obtain a follow-up CT scan or MRI at 24 hours before starting anticoagulants or antiplatelet agents.

Continue to monitor for signs of hypersensitivity
Indication

Activase® (alteplase) is indicated for the treatment of acute ischemic stroke (AIS). Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment. Initiate treatment as soon as possible but within 3 hours after symptom onset.

Important Safety Information

Contraindications

Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit: current intracranial hemorrhage (ICH); subarachnoid hemorrhage; active internal bleeding; recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms); bleeding diathesis; and current severe uncontrolled hypertension.
Important Safety Information

Warnings and Precautions

Bleeding

Activase can cause significant, sometimes fatal internal or external bleeding, especially at arterial and venous puncture sites. Avoid intramuscular injections and trauma to the patient. Perform venipunctures carefully and only as required. Fatal cases of hemorrhage associated with traumatic intubation in patients administered Activase have been reported. The concomitant administration of heparin and aspirin with and following infusions of Activase for the treatment of AIS during the first 24 hours after symptom onset has not been investigated. Because heparin, aspirin, or Activase may cause bleeding complications, carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of Activase, while patients are still receiving anticoagulant therapy. If serious bleeding occurs, terminate the Activase infusion, and treat properly.

Please see select Important Safety Information throughout and the full Prescribing Information below.
**Warnings and Precautions**

**Bleeding (cont’d)**

In the following conditions, the risks of bleeding with Activase® (alteplase) are increased and should be weighed against the anticipated benefits: recent major surgery or procedure; cerebrovascular disease; recent intracranial hemorrhage; recent gastrointestinal or genitourinary bleeding; recent trauma; hypertension; acute pericarditis; subacute bacterial endocarditis; hemostatic defects including those secondary to severe hepatic or renal disease; significant hepatic dysfunction; pregnancy; diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions; septic thrombophlebitis or occluded AV cannula at seriously infected site; advanced age; and patients currently receiving oral anticoagulants, or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.
Warnings and Precautions

Hypersensitivity

Hypersensitivity, including urticarial/anaphylactic reactions, have been reported after administration of Activase. Rare fatal outcome for hypersensitivity was reported. Angioedema has been observed during and up to 2 hours after infusion in patients treated for acute ischemic stroke and acute myocardial infarction. In many cases, patients received concomitant angiotensin-converting enzyme inhibitors. Monitor patients during and for several hours after infusion for hypersensitivity. If signs of hypersensitivity occur, e.g. anaphylactoid reaction or angioedema develops, discontinue the Activase infusion and promptly institute appropriate therapy (e.g., antihistamines, intravenous corticosteroids, epinephrine).

Please see select Important Safety Information throughout and the full Prescribing Information below.
Important Safety Information

**Warnings and Precautions**

*Thromboembolism*

The use of thrombolytics can increase the risk of thrombo-embolic events in patients with high likelihood of left heart thrombus, such as patients with mitral stenosis or atrial fibrillation. Activase® (alteplase) has not been shown to treat adequately underlying deep vein thrombosis in patients with PE. Consider the possible risk of re-embolization due to the lysis of underlying deep venous thrombi in this setting.

*Cholesterol Embolization*

Cholesterol embolism, sometimes fatal, has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown. It is associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy.
Warnings and Precautions

Coagulation Tests May Be Unreliable During Activase Therapy

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

Adverse Reactions

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

Please see select Important Safety Information throughout and the full Prescribing Information below.
References (cont’d)


