TNKase® STROKE ASSESSMENT
EDUCATION GUIDE

Indication

Acute Ischemic Stroke

TNKase (tenecteplase) is indicated for the treatment of acute ischemic stroke (AIS) in adults.

✓ FDA APPROVED

TNKase® Single-Bolus Tenecteplase

Important Safety Information

Contraindications

TNKase is contraindicated in any patients with:

- Active internal bleeding
- Intracranial or intraspinal surgery or trauma within 2 months
- Known bleeding diathesis
- Current severe uncontrolled hypertension
- Presence of intracranial conditions that may increase the risk of bleeding (eg, intracranial neoplasm, arteriovenous malformation, or aneurysm)

TNKase is also contraindicated in patients for the treatment of AIS with:

- Active intracranial hemorrhage

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

Genentech
A Member of the Roche Group

Assessing and treating AIS

A resource for managing AIS, from presentation through TNKase administration

Find details about:

Clinical presentation

See signs and symptoms associated with AIS, along with differential diagnoses

Individualized stroke assessment

Look beyond the NIHSS for a comprehensive evaluation of disability

Treating with TNKase

Get details on patient selection, dosing, and post-administration monitoring

TNKase® (tenecteplase) single-bolus

AIS=acute ischemic stroke; NIHSS=National Institutes of Health Stroke Scale.

Please see Important Safety Information on pages 20-22 and the full Prescribing Information.

Clinical presentation of AIS

Common symptoms of anterior circulation stroke include[1]:

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

Some symptoms of posterior circulation stroke include[2,3]:

- Diplopia
- Dizziness
- Dysarthria
- Dysphagia
- Dystaxia or ataxia

Conditions that may mimic stroke[4]*:

- Bell's Palsy
- Complicated migraine
- Conversion disorder or psychogenic conditions
- Hypertensive encephalopathy
- Hypoglycemia
- Infection or abscess
- Seizures
- Tumor

*The listed conditions that may mimic stroke are not exhaustive.
AIS=acute ischemic stroke.

NIHSS[5]

CATEGORY	DESCRIPTION	SCORE
1a. Level of Consciousness (LOC) (Is the patient alert, drowsy, etc?)	Alert; keenly responsive Arousable by minor stimulation Requires repeated or strong/painful stimulation Unresponsive or reflex responses only	**0** **1** **2** **3**
1b. LOC Questions (Ask the patient the month and his or her age. Answer must be correct.)	Answers both correctly Answers one correctly Both incorrect	**0** **1** **2**
1c. LOC Commands (Ask patient to open/close eyes and then grip/release nonparetic hand.)	Performs both correctly Performs one correctly Both incorrect	**0** **1** **2**
2. Best Gaze (Only horizontal movement tested. Oculocephalic reflex is scored, but not calorics. Eyes open—patient follows finger or face.)	Normal Partial gaze palsy Forced deviation	**0** **1** **2**
3. Visual Fields (Test by confrontation. Introduce visual stimulus to patient's upper- and lower-field quadrants.)	No visual loss Partial hemianopia Complete hemianopia Bilateral hemianopia	**0** **1** **2** **3**
4. Facial Palsy (Ask patient to show teeth/smile, raise eyebrows, and close eyes.)	Normal Minor paralysis Partial paralysis Complete paralysis	**0** **1** **2** **3**
5. Motor Arm (Alternately position the patient's arms. Extend arm 90 degrees [if sitting] or 45 degrees [if supine].)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation or joint fusion	**0** **1** **2** **3** **4** **UN**

NIHSS=National Institutes of Health Stroke Scale; UN=untestable.

NIHSS[5] (cont'd)

CATEGORY	DESCRIPTION	SCORE
6. Motor Leg (Alternately position the patient's legs. Extend each leg 30 degrees, always while supine.)	No drift Drift Some effort against gravity No effort against gravity No movement Amputation or joint fusion	**0** **1** **2** **3** **4** **UN**
7. Limb Ataxia (finger-nose-finger, heel-shin tests done on both sides.)	Absent Present in one limb Present in two limbs Amputation or joint fusion	**0** **1** **2** **UN**
8. Sensory (Use a pinprick to face, arms, trunk, and legs—compare side to side. Assess patient's awareness of being touched.)	Normal Mild-to-moderate loss Severe or total loss	**0** **1** **2**
9. Best Language (Ask patient to name items, describe a picture, read a sentence; intubated patients should write responses.)	No aphasia Mild-to-moderate aphasia Severe aphasia Mute, global aphasia	**0** **1** **2** **3**
10. Dysarthria (Evaluate speech clarity by asking patient to repeat listed words.)	Normal articulation Mild-to-moderate dysarthria Severe dysarthria Intubated or other physical barrier	**0** **1** **2** **UN**
11. Extinction and Inattention (Use information from prior testing to identify neglect.)	No abnormality Partial inattention or extinction Profound hemi-inattention or extinction	**0** **1** **2**

NIHSS=National Institutes of Health Stroke Scale; UN=untestable.

Patients with AIS may initially be misdiagnosed[6]

A retrospective chart review found 1 in 5 ischemic strokes was initially misdiagnosed (n=103/465).

Not all disability deficits may be detected by the NIHSS

- Although the NIHSS is a useful tool for rating the level of neurological deficit due to stroke, it does not measure all deficits, nor does it fully assess the impact of disability on a patient's daily living or activity.[7-9]
  - Use of the NIHSS should not substitute for a comprehensive neurological examination[7-9]
- The NIHSS is recommended by the 2019 American Heart Association/American Stroke Association (AHA/ASA) to quantify the degree of neurological deficit with accuracy and reliability[7]
- The NIHSS was originally developed for stroke research trials[10]
- Studies indicate that the NIHSS grades lesion-specific deficits unevenly[9]

AIS=acute ischemic stroke; NIHSS=National Institutes of Health Stroke Scale.

Consider how individual deficits are potentially disabling

While the NIHSS can rate the level of neurological deficit due to stroke, it may not detect all 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.[7,9]

The TNKase (tenecteplase) clinical trial enrolled patients with a measurable neurological deficit.[11]

Deficits considered by the AHA/ASA to be disabling[8]:

- Complete hemianopsia (≥2 on NIHSS question 3) or 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 6 or 7)
- Any deficits that lead to a total NIHSS score >5
- Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required

AHA/ASA=American Heart Association/American Stroke Association; NIHSS=National Institutes of Health Stroke Scale.

Important Safety Information (cont'd)
Warnings and Precautions
Bleeding

TNKase can cause significant, sometimes fatal, internal or external bleeding, especially at arterial and venous puncture sites. Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. Avoid intramuscular injections and trauma to the patient while on TNKase. Perform arterial and venous punctures carefully and only as required. To minimize bleeding from noncompressible sites, avoid internal jugular and subclavian venous punctures. If an arterial puncture is necessary during TNKase administration, use an upper extremity vessel that is accessible to manual compression, apply pressure for at least 30 minutes, and monitor the puncture site closely. Should serious bleeding that is not controlled by local pressure occur, discontinue any concomitant heparin or antiplatelet agents immediately and treat appropriately.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

Determine if your patients' deficits are potentially disabling

Consider the following:

- Is your patient able to ambulate independently?
- Are they able to speak and understand?
- Are they able to hold a conversation? Are there signs of altered mental status?

Consider asking each patient 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?
- What is your dominant hand? Will weakness of your hand affect your daily life?
- Do you think your quality of life will be impacted?

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.[12] The modified Rankin Scale measures the ability of a patient to function independently without assistance.[13]

Modified Rankin Scale[13]:

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Death

AHA/ASA Guidelines for use of thrombolytics

AHA/ASA 2019 update to the 2018 Guidelines recommend thrombolytics for management of AIS[7]

IV Activase® (alteplase) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient's 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)**.

It may be reasonable to choose [TNKase®] tenecteplase (single [5-second] IV bolus ..., maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy **(Class IIb; Level of Evidence B-R)**.*

SVIN 2022 Recommendations[14]

- Current data do not favor mechanical thrombectomy alone in patients who meet the criteria for intravenous thrombolysis (IVT). Premechanical thrombectomy IVT in patients with emergent large vessel occlusion ischemic stroke, combined with mechanical thrombectomy, is recommended for eligible patients and should not be skipped in favor of mechanical thrombectomy alone **(Class 1; Level of Evidence A)**.

*Since the guidelines were published in 2019, TNKase has received FDA approval for the treatment of AIS in adults.
AHA/ASA=American Heart Association/American Stroke Association; AIS=acute ischemic stroke; Class I=is recommended; Class IIb=may be considered; IV=intravenous; Level of Evidence A=high-quality evidence from more than one randomized controlled trial; Level of Evidence B-R=moderate-quality evidence from one or more randomized controlled trial; LVO=large vessel occlusion; SVIN=Society of Vascular and Interventional Neurology.

Indication for Activase (alteplase)

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 for Activase (alteplase)

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 additional Important Safety Information for Activase on pages 23 and 24 and the full Prescribing Information.

Important Safety Information for TNKase (tenecteplase) (cont'd)

Warnings and Precautions (cont'd)

Bleeding (cont'd)

The concomitant administration of heparin and aspirin with and following administration of TNKase for the treatment of acute ischemic stroke during the first 24 hours after symptom onset has not been investigated.

Please see additional Important Safety Information for TNKase on pages 20-22 and the full Prescribing Information.

Assess TNKase eligibility for patients presenting with acute ischemic stroke

Baseline functional status and neurological deficits should be considered in the context of individual risk and benefit when establishing eligibility for TNKase[7]

TNKase is indicated for the treatment of AIS in adults[11]

Do not administer TNKase in patients with contraindications and if the risk of bleeding is greater than the potential benefit[11]

AIS=acute ischemic stroke.

Important Safety Information (cont'd)

Contraindications

TNKase is contraindicated in any patients with:

- Active internal bleeding
- Intracranial or intraspinal surgery or trauma within 2 months
- Known bleeding diathesis
- Current severe uncontrolled hypertension
- Presence of intracranial conditions that may increase the risk of bleeding (eg, intracranial neoplasm, arteriovenous malformation, or aneurysm)

TNKase is also contraindicated in patients for the treatment of AIS with:

- Active intracranial hemorrhage

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

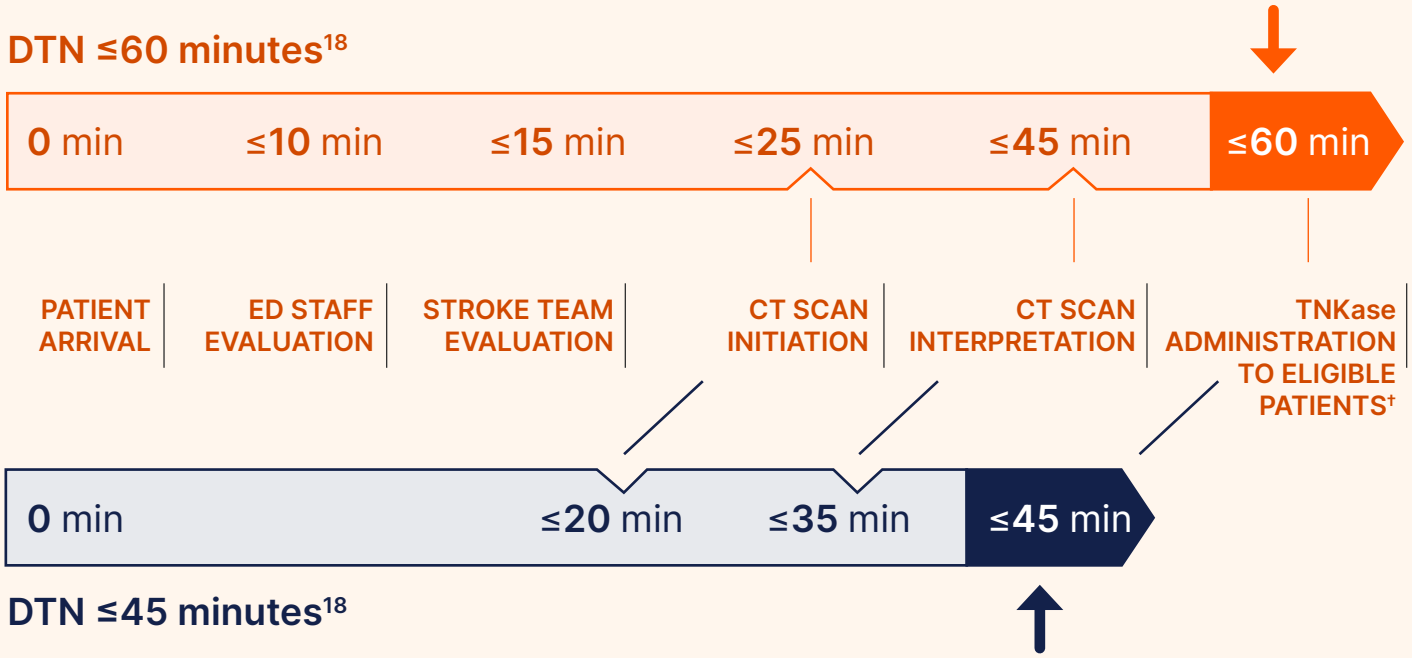
TNKase® (tenecteplase) Single-bolus

National recommendations: Door-to-needle (DTN) times for AIS[15]

The Joint Commission requires DTN of ≤60 minutes in at least 50% of all eligible AIS patients receiving thrombolytics[15,16]

Target: Stroke* has established a more aggressive goal[17]:

- DTN within 60 minutes in at least 85% of patients
- DTN within 45 minutes in at least 75% of patients
- DTN within 30 minutes in at least 50% of patients

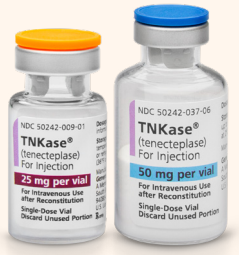


*Target: Stroke is a national initiative by the AHA/ASA to improve stroke outcomes.[17]
†Initiate treatment with TNKase as soon as possible within 3 hours of symptom onset.[11]
AIS=acute ischemic stroke; CT=computed tomography; ED=emergency department.

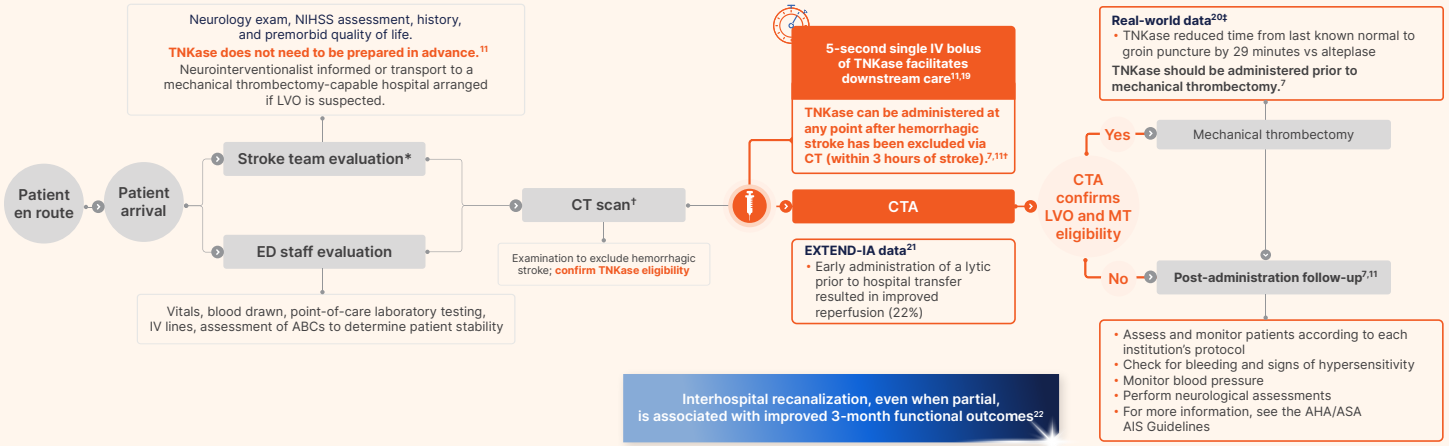
Please see Important Safety Information on pages 20-22 and the full Prescribing Information.

TNKase® (tenecteplase) Single-bolus

TNKase helps streamline the treatment pathway for patients with acute ischemic stroke



Administration of the TNKase (tenecteplase) 5-second IV bolus can facilitate rapid patient transport and can allow the stroke treatment team to focus on other aspects of care[19]



*Certain patient evaluations and diagnoses may be performed using telestroke services.[7]
†As an alternative to a CT scan, an MRI may also be used.
‡Retrospective analysis of acute ischemic stroke patients aged >18 years who received IVT and underwent EVT between January 2020 and June 2023 (N=635). Patients either received alteplase (0.9 mg/kg) or TNKase (0.25 mg/kg) and were then referred for EVT.[20]

ABCs=airway, breathing, and circulation; AHA/ASA=American Heart Association/American Stroke Association; AIS=acute ischemic stroke; CT=computed tomography; CTA=computed tomography angiography; ED=emergency department; EVT=endovascular thrombectomy; IVT=intravenous thrombolysis; LVO=large vessel occlusion; MRI=magnetic resonance imaging; MT=mechanical thrombectomy; NIHSS=National Institutes of Health Stroke Scale.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Bleeding (cont'd)

Because heparin, aspirin, or TNKase may cause bleeding complications, carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of TNKase, while patients are still receiving anticoagulant therapy.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

TNKase® (tenecteplase) Single-Bolus

FDA-approved dosing of TNKase for AIS[11]

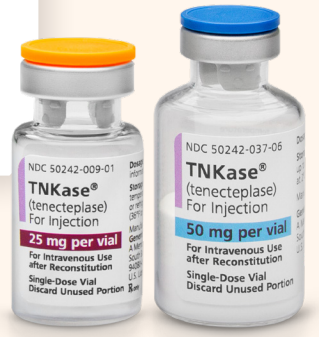
- TNKase is for intravenous (IV) administration only, administered as a single bolus over 5 seconds

Initiate treatment as soon as possible within 3 hours of symptom onset

Recommended dosage for AIS:

Patient weight (kg)	TNKase (mg)	Volume TNKase to be administered (mL)
<60 kg	15 mg	3 mL
≥60 to <70 kg	17.5 mg	3.5 mL
≥70 to <80 kg	20 mg	4 mL
≥80 to <90 kg	22.5 mg	4.5 mL
≥90 kg	25 mg	5 mL

Individualize dosing based on patient's weight per table above.
The maximum recommended dose is 25 mg (5 mL).



AIS=acute ischemic stroke; FDA=US Food and Drug Administration.

Important Safety Information (cont'd)
Warnings and Precautions (cont'd)
Bleeding (cont'd)

In the following conditions, the risks of bleeding with TNKase therapy for all approved indications are increased and should be weighed against the anticipated benefits: recent major surgery or procedure, (eg, coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels); cerebrovascular disease; recent intracranial hemorrhage (if not contraindicated); recent gastrointestinal or genitourinary bleeding; recent trauma; hypertension: systolic BP above 175 mm Hg or diastolic BP above 110 mm Hg; 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; patients currently receiving anticoagulants; or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

TNKase Tenecteplase Single-Bolus

Blood glucose management in patients with AIS[7]

Recommendations from AHA/ASA 2019 update to the 2018 Guidelines

- 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)**

AHA/ASA=American Heart Association/American Stroke Association; AIS=acute ischemic stroke; Class I=is recommended; Class IIa=procedure can be considered effective (moderate strength; benefit can be greater than risk); Level C-LD=limited data available to support the recommendation.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Hypersensitivity

Hypersensitivity, including urticarial/anaphylactic reactions, have been reported after administration of TNKase (eg, anaphylaxis, angioedema, laryngeal edema, rash, and urticaria). Monitor patients treated with TNKase during and for several hours after administration. If symptoms of hypersensitivity occur, initiate appropriate therapy (eg, antihistamines, corticosteroids, or epinephrine).

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

TNKase Single-Bolus Tenecteplase

Blood pressure (BP) management in patients with AIS

Recommendations from AHA/ASA 2019 update to the 2018 Guidelines[7]

If patients are otherwise eligible for acute reperfusion 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, titrate by doubling the dose every 2-5 minutes until desired BP reached, maximum 21 mg/h or
- Other agents (eg, hydralazine, enalaprilat) may also be considered

If serious bleeding occurs, treat appropriately. For patients with hypertension, BP above 175 mm Hg or diastolic BP above 110 mm Hg, the risks of bleeding with tenecteplase use are increased and should be weighed against the anticipated benefits.[11]

BP management in patients with AIS[7]

- 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 thrombolytics 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)**

AHA/ASA=American Heart Association/American Stroke Association; AIS=acute ischemic stroke; Class I=is recommended; Class IIb=is reasonable; IV=intravenous; Level C-EO=consensus of expert opinion based on clinical experience.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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.

Cholesterol Embolization

Cholesterol embolism has been reported in patients treated with thrombolytic agents. Investigate cause of any new embolic event and treat appropriately.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

Patient monitoring during TNKase administration[11]

- During and following TNKase administration for the treatment of acute ischemic stroke, frequently monitor and control blood pressure
- In patients without recent use of oral anticoagulants or heparin, TNKase treatment can be initiated prior to the availability of coagulation study results. If the pretreatment international normalized ratio (INR) is greater than 1.7 or the activated partial thromboplastin time (aPTT) is elevated, closely monitor patients

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that anti-arrhythmic therapy for bradycardia and/or ventricular irritability be available when TNKase is administered.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

Patient monitoring post-TNKase administration[11]

- Assess and monitor patients according to each institution's protocol

Monitor for bleeding

- TNKase, heparin, or aspirin may cause bleeding complications; carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of TNKase, while patients are still receiving anticoagulant therapy

Continue to monitor for signs of hypersensitivity

- Monitor patients during and several hours after administration for signs of hypersensitivity, administering appropriate therapy (eg, antihistamines, corticosteroids, epinephrine)

Important Safety Information (cont'd)

Adverse Reactions

The most common adverse reaction is bleeding.

Drug Interactions

Drug/Laboratory Test Interactions

During TNKase therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Tenecteplase is an enzyme that, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

TNKase Single-Bolus Tenecteplase

Patient monitoring based on AHA/ASA guidelines for Activase[7]

Monitor for neurological deterioration

- Every 15 minutes for the first 2 hours after administration
- Every 30 minutes for the next 6 hours
- Hourly until 24 hours after administration

Monitor and control BP

- Every 15 minutes for the first 2 hours after administration
- Every 30 minutes for the next 6 hours
- Hourly until 24 hours after administration

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

- For more information, see the 2019 update to the 2018 AHA/ASA AIS Guidelines

AHA/ASA=American Heart Association/American Stroke Association; AIS=acute ischemic stroke; BP=blood pressure; CT=computed tomography; MRI=magnetic resonance imaging.

Important Safety Information (cont'd)

Patient Counseling Information

Bleeding

Inform patients that bleeding can occur 1 or more days after administration of TNKase. Instruct patients to contact a healthcare provider if they experience signs or symptoms consistent with bleeding (eg, unusual bruising; pink or brown urine; red, black, or tarry stools; coughing up blood; vomiting blood or blood that looks like coffee grounds) or symptoms of a stroke.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see additional Important Safety Information on pages 20-22 and the full Prescribing Information.

TNKase® (tenecteplase) Single-bolus

Indication and Important Safety Information for TNKase (tenecteplase)

Indication

Acute Ischemic Stroke

TNKase (tenecteplase) is indicated for the treatment of acute ischemic stroke (AIS) in adults.

Important Safety Information

Contraindications

TNKase is contraindicated in any patients with:

- Active internal bleeding
- Intracranial or intraspinal surgery or trauma within 2 months
- Known bleeding diathesis
- Current severe uncontrolled hypertension
- Presence of intracranial conditions that may increase the risk of bleeding (eg, intracranial neoplasm, arteriovenous malformation, or aneurysm)

TNKase is also contraindicated in patients for the treatment of AIS with:

- Active intracranial hemorrhage

Please see additional Important Safety Information on pages 21 and 22 and the full Prescribing Information.

Important Safety Information for TNKase (cont'd)

Warnings and Precautions

Bleeding

TNKase can cause significant, sometimes fatal, internal or external bleeding, especially at arterial and venous puncture sites. Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. Avoid intramuscular injections and trauma to the patient while on TNKase. Perform arterial and venous punctures carefully and only as required. To minimize bleeding from noncompressible sites, avoid internal jugular and subclavian venous punctures. If an arterial puncture is necessary during TNKase administration, use an upper extremity vessel that is accessible to manual compression, apply pressure for at least 30 minutes, and monitor the puncture site closely. Should serious bleeding that is not controlled by local pressure occur, discontinue any concomitant heparin or antiplatelet agents immediately and treat appropriately.

The concomitant administration of heparin and aspirin with and following administration of TNKase for the treatment of acute ischemic stroke during the first 24 hours after symptom onset has not been investigated. Because heparin, aspirin, or TNKase may cause bleeding complications, carefully monitor for bleeding, especially at arterial puncture sites. Hemorrhage can occur 1 or more days after administration of TNKase, while patients are still receiving anticoagulant therapy.

In the following conditions, the risks of bleeding with TNKase therapy for all approved indications are increased and should be weighed against the anticipated benefits: recent major surgery or procedure, (eg, coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels); cerebrovascular disease; recent intracranial hemorrhage (if not contraindicated); recent gastrointestinal or genitourinary bleeding; recent trauma; hypertension: systolic BP above 175 mm Hg or diastolic BP above 110 mm Hg; 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; patients currently receiving anticoagulants; or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Hypersensitivity

Hypersensitivity, including urticarial/anaphylactic reactions, have been reported after administration of TNKase (eg, anaphylaxis, angioedema, laryngeal edema, rash, and urticaria). Monitor patients treated with TNKase during and for several hours after administration. If symptoms of hypersensitivity occur, initiate appropriate therapy (eg, antihistamines, corticosteroids, or epinephrine).

Please see additional Important Safety Information on pages 20 and 22 and the full Prescribing Information.

Important Safety Information for TNKase (cont'd)

Warnings and Precautions (cont'd)

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.

Cholesterol Embolization

Cholesterol embolism has been reported in patients treated with thrombolytic agents. Investigate cause of any new embolic event and treat appropriately.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that anti-arrhythmic therapy for bradycardia and/or ventricular irritability be available when TNKase is administered.

Adverse Reactions

The most common adverse reaction is bleeding.

Drug Interactions

Drug/Laboratory Test Interactions

During TNKase therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Tenecteplase is an enzyme that, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis.

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You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see the full Prescribing Information for additional Important Safety Information.

TNKase Single-bolus Tenecteplase

Indication and Important Safety Information for Activase (alteplase)

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.

Warnings and Precautions

Bleeding

Activase can cause significant, and sometimes fatal internal or external bleeding. 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. Heparin, aspirin, or Activase may cause bleeding complications; therefore, carefully monitor for bleeding. If serious bleeding occurs, terminate the Activase infusion, and treat appropriately.

Hypersensitivity

Hypersensitivity, including urticarial/anaphylactic reactions, have been reported. Rare fatal outcome for hypersensitivity was reported. Angioedema has been observed during and up to 2 hours after Activase 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 additional Important Safety Information on page 24 and the full Prescribing Information.

TNKase Tenecteplase Single-Bolus

Important Safety Information for Activase (cont'd)

Warnings and Precautions (cont'd)

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 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.

Coagulation Tests May be Unreliable during Activase Therapy

Coagulation tests and/or measures of fibrinolytic activity may be unreliable during Activase therapy.

Adverse Reactions

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

Please see the full Prescribing Information for additional Important Safety Information.

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