TNKASE- tenecteplase
Genentech, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TNKASE safely and effectively. See full prescribing information for TNKASE.

TNKase (tenecteplase) for injection, for intravenous use
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Warnings and Precautions (5.1)	xx/202x

INDICATIONS AND USAGE

TNKase is a tissue plasminogen activator, indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms. (1)

DOSAGE AND ADMINISTRATION

- TNKase® is for intravenous administration only. The recommended total dose is based upon patient weight, not to exceed 50 mg. (2.1)
- Administer a single bolus dose over 5 seconds based on patient weight. Initiate treatment as soon as possible after the onset of AMI symptoms. (2.1)

DOSAGE FORMS AND STRENGTHS

- Lyophilized powder: 50 mg with Sterile Water for Injection USP for reconstitution at 5 mg per 1 mL. (3)

CONTRAINDICATIONS

- Active internal bleeding (4)
- History of cerebrovascular accident (4)
- Intracranial or intraspinal surgery or trauma within 2 months (4)
- Intracranial neoplasm, arteriovenous malformation, or aneurysm (4)
- Known bleeding diathesis (4)
- Severe uncontrolled hypertension (4)

WARNINGS AND PRECAUTIONS

- Bleeding: Increases the risk of bleeding. Avoid intramuscular injections. Monitor for bleeding. (5.1)
- Thromboembolism: The use of thrombolytics can increase the risk of thrombo-embolic events in patients with high likelihood of left heart thrombus. (5.2)
- Cholesterol Embolization: Has been reported rarely in patients treated with all types of thrombolytic agents. (5.3)
- Arrhythmias: It is recommended that anti-arrhythmic therapy for bradycardia and/or ventricular irritability be available when TNKase is administered. (5.4)
- Use with Percutaneous Coronary Intervention (PCI): In patients with large ST segment elevation myocardial infarction, physicians should choose either thrombolysis or PCI as the primary treatment strategy for reperfusion. Rescue PCI or subsequent elective PCI may be performed after administration of thrombolytic therapies if medically appropriate. (5.5)
- Hypersensitivity: Monitor patients treated with TNKase during and for several hours after infusion. If symptoms of hypersensitivity occur, initiate appropriate therapy (e.g. antihistamines, corticosteroids). (5.6)

ADVERSE REACTIONS

The most common adverse reactions are bleeding and hypersensitivity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Roche at 1-800-526-6367 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Anticoagulants and drugs that inhibit platelet function increase the risk of bleeding when administered with TNKase therapy. (7)
- 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. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TNKase® is indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

TNKase® is for intravenous administration only. The recommended total dose is based upon patient weight, not to exceed 50 mg (*see* Table 1).

Administer a single bolus dose over 5 seconds based on patient weight. Initiate treatment as soon as possible after the onset of AMI symptoms *[see Clinical Studies (14.1)]*.

Table 1 Dose Information Table

Patient Weight (kg)	TNKase (mg)	Volume TNKase* to be administered (mL)
< 60	30	6
≥ 60 to < 70	35	7
≥ 70 to < 80	40	8
≥ 80 to < 90	45	9
≥ 90	50	10

* From one vial of TNKase reconstituted with 10 mL SWFI.

The safety and efficacy of TNKase have only been investigated with concomitant administration of heparin and aspirin as described in *Clinical studies (14.1)*.

2.2 Reconstitution

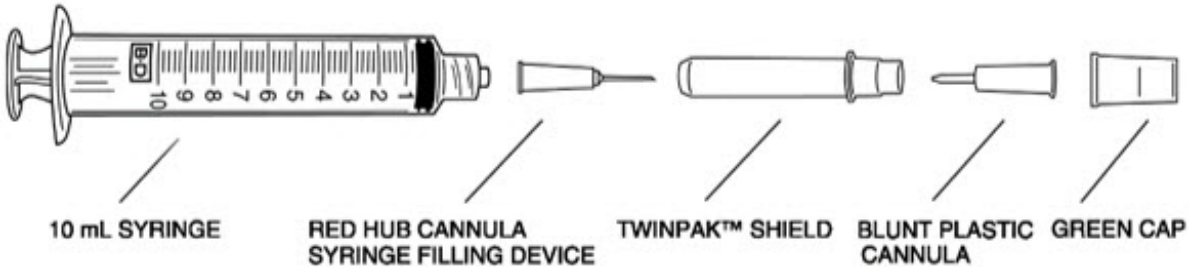
NOTE: Read all instructions completely before beginning reconstitution and administration. Use aseptic technique.

- Remove the shield assembly from the supplied B-D® 10 mL syringe with TwinPak™ Dual Cannula Device (see Figure 1) and aseptically withdraw 10 mL of Sterile Water for Injection (SWFI), USP, from the supplied diluent vial using the red hub cannula syringe filling device. Do not use Bacteriostatic Water for Injection, USP.

- Note: Do not discard the shield assembly.
- Inject the entire contents of the syringe (10 mL) into the TNKase vial directing the diluent stream into the powder. Slight foaming upon reconstitution is not unusual; any large bubbles will dissipate if the product is allowed to stand undisturbed for several minutes.
- Gently swirl until contents are completely dissolved. DO NOT SHAKE. The reconstituted preparation results in a colorless to pale yellow transparent solution containing TNKase at 5 mg/mL at a pH of approximately 7.3. The osmolality of this solution is approximately 290 mOsm/kg.
- Determine the appropriate dose of TNKase *[see Dosage and Administration (2.1)]* and withdraw this volume (in milliliters) from the reconstituted vial with the syringe. **Discard any unused solution.**
- Once the appropriate dose of TNKase is drawn into the syringe, stand the shield vertically on a flat surface (with green side down) and passively recap the red hub cannula.
- Remove the entire shield assembly, including the red hub cannula, by twisting counterclockwise. Note: The shield assembly also contains the clear-ended blunt plastic cannula; retain for split septum IV access.

Figure 1

The B-D® 10 mL Syringe with TwinPak™ Dual Cannula Device



2.3 Administration

- Visually inspect the product prior to administration for particulate matter and discoloration. Administer TNKase as reconstituted at 5 mg/mL.
- Precipitation may occur when TNKase is administered in an IV line containing dextrose. Flush dextrose-containing lines with a saline-containing solution prior to and following single bolus administration of TNKase.
- Administer reconstituted TNKase as a single IV bolus over 5 seconds.
- Because TNKase contains no antibacterial preservatives, reconstitute immediately before use. If the reconstituted TNKase is not used immediately, refrigerate the TNKase vial at 2–8°C (36–46°F) and use within 8 hours.
- Although the supplied syringe is compatible with a conventional needle, this syringe is designed to be used with needleless IV systems. From the information below, follow the instructions applicable to the IV system in use.

  - Remove the green cap.
  - Attach the clear-

Split septum IV system:	ended blunt plastic cannula to the syringe. • Remove the shield and use the blunt plastic cannula to access the split septum injection port. • Because the blunt plastic cannula has two side ports, air or fluid expelled through the cannula will exit in two sideways directions; direct away from face or mucous membranes.
Luer-Lok® system:	Connect syringe directly to IV port.
Conventional needle (not supplied in this kit):	Attach a large bore needle, e.g., 18 gauge, to the syringe's universal Luer-Lok®.

- Dispose of the syringe, cannula and shield per established procedures.

3 DOSAGE FORMS AND STRENGTHS

50 mg lyophilized powder per single use vial with 10 mL SWFI USP for reconstitution at 5 mg per 1 mL

4 CONTRAINDICATIONS

TNKase therapy in patients with acute myocardial infarction is contraindicated in the following situations because of an increased risk of bleeding *[see Warnings and Precautions (5.1)]*:

- Active internal bleeding
- History of cerebrovascular accident
- Intracranial or intraspinal surgery or trauma within 2 months
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled hypertension

5 WARNINGS AND PRECAUTIONS

General

Each patient being considered for therapy with TNKase should be carefully evaluated and

anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risk of TNKase therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects, including those secondary to severe hepatic or renal disease
- Severe hepatic dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age *[see Geriatric Use (8.5)]*
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Recent administration of GP IIb/IIIa inhibitors
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

5.1 Bleeding

The most common complication encountered during TNKase therapy is bleeding. Sites of bleeding include both internal and superficial bleeding sites. Intracranial hemorrhage has been observed in patients treated with TNKase *[see Adverse Reactions (6)]*.

Heparin and aspirin have been administered with TNKase in clinical trials and heparin may play a role in serious bleeding incidence. The safety of the use of TNKase with other antiplatelets has not been adequately studied *[see Drug Interactions (7.1)]*. Careful monitoring for bleeding is advised.

Should serious bleeding (not controlled by local pressure) occur, discontinue any concomitant heparin or antiplatelet agents immediately and treat appropriately.

Avoid intramuscular injections and nonessential handling of the patient for the first few hours following treatment with 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 infusion, use an upper extremity vessel that is accessible to manual compression. Apply pressure for at least 30 minutes. Check the pressure dressing applied, and the puncture site frequently for evidence of bleeding.

5.2 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.

5.3 Cholesterol Embolization

Cholesterol embolism 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.

5.4 Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) may be managed with standard anti-arrhythmic measures. It is recommended that anti-arrhythmic therapy for bradycardia and/or ventricular irritability be available when TNKase is administered.

5.5 Use with Percutaneous Coronary Intervention (PCI)

In patients with large ST segment elevation myocardial infarction, physicians should choose either thrombolysis or PCI as the primary treatment strategy for reperfusion. Rescue PCI or subsequent elective PCI may be performed after administration of thrombolytic therapies if medically appropriate; however, the optimal use of adjunctive antithrombotic and antiplatelet therapies in this setting is unknown.

5.6 Hypersensitivity

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

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of TNKase were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions are also discussed in other sections of the label:

- Bleeding *[see Contraindications (4), Warnings and Precautions (5.1)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class.

Table 2 displays the frequency of adverse reactions

System organ class	Reported frequency	Adverse reaction
Vascular disorders	Very common (≥1/10)	Hemorrhage
	Rare	

	(≥1/10,000 to <1/1,000)	Embolism (thrombotic embolization)
Skin and subcutaneous tissue disorders	Common (≥1/100 to <1/10)	Ecchymosis
Renal and urinary disorders	Common (≥1/100 to <1/10)	Urogenital hemorrhage (such as hematuria, urinary tract hemorrhage)
General disorders and administration site conditions	Common (≥1/100 to <1/10)	Injection site hemorrhage, puncture site hemorrhage
Gastrointestinal disorders	Common (≥1/100 to <1/10)	Gastrointestinal hemorrhage (such as gastric hemorrhage, gastric ulcer hemorrhage, rectal hemorrhage, hematemesis, melena, mouth hemorrhage)
	Uncommon (≥1/1,000 to <1/100)	Retroperitoneal hemorrhage (such as retroperitoneal hematoma)
	Not known (cannot be estimated from the available data)	Nausea, vomiting
Respiratory, thoracic and mediastinal disorders	Common (≥1/100 to <1/10)	Epistaxis
	Rare (≥1/10,000 to <1/1,000)	Pulmonary hemorrhage
Nervous system disorders	Uncommon (≥1/1,000 to <1/100)	Intracranial hemorrhage (such as cerebral hemorrhage, cerebral hematoma, hemorrhagic stroke, hemorrhagic transformation stroke, intracranial hematoma, subarachnoid hemorrhage) including associated symptoms as somnolence, aphasia, hemiparesis, convulsion
Eye disorders	Uncommon (≥1/1,000 to <1/100)	Eye hemorrhage
Cardiac disorders	Uncommon (≥1/1,000 to <1/100)	Reperfusion arrhythmias (such as asystole, accelerated idioventricular arrhythmia, arrhythmia, extrasystoles, atrial fibrillation, atrioventricular first degree to atrioventricular block complete, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia) occur in close temporal relationship to treatment with tenecteplase. Reperfusion arrhythmias may lead to

		cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.
	Rare (≥1/10,000 to <1/1,000)	Pericardial hemorrhage
Immune system disorders	Rare (≥1/10,000 to <1/1,000)	Anaphylactoid reaction (including rash, urticaria, bronchospasm, laryngeal edema)
Investigations	Rare (≥1/10,000 to <1/1,000)	Blood pressure decreased
	Not known (cannot be estimated from the available data)	Body temperature increased
Injury, poisoning and procedural complications	Not known (cannot be estimated from the available data)	Fat embolism, which may lead to corresponding consequences in the organs concerned

As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and/or thrombolytic administration:

- very common: hypotension, heart rate and rhythm disorders, angina pectoris
- common: recurrent ischemia, cardiac failure, myocardial infarction, cardiogenic shock, pericarditis, pulmonary edema
- uncommon: cardiac arrest, mitral valve incompetence, pericardial effusion, venous thrombosis, cardiac tamponade, myocardial rupture
- rare: pulmonary embolism

These cardiovascular events can be life-threatening and may lead to death.

6.1 Immunogenicity

Four of 625 (0.64%) patients tested for antibody formation to TNKase had a positive antibody titer at 30 days [TIMI10A and TIMI 10B]. The observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TNKase with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Drug Interactions

Formal interaction studies of TNKase with other drugs have not been performed. Patients studied in clinical trials of TNKase were routinely treated with heparin and aspirin. Anticoagulants (such as heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and GP IIb/IIIa inhibitors) may

increase the risk of bleeding if administered prior to, during, or after TNKase therapy.

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TNKase has been shown to elicit maternal and embryo toxicity in rabbits given multiple IV administrations. In rabbits administered 0.5, 1.5, and 5.0 mg/kg/day during organogenesis, vaginal hemorrhage resulted in maternal deaths. Subsequent embryonic deaths were secondary to maternal hemorrhage and no fetal anomalies were observed. TNKase does not elicit maternal and embryo toxicity in rabbits following a single IV administration. Thus, in developmental toxicity studies conducted in rabbits, the no observable effect level (NOEL) of a single IV administration of TNKase on maternal or developmental toxicity (5 mg/kg) was approximately 7 times human exposure (based on AUC) at the dose for AMI. There are no adequate and well-controlled studies in pregnant women. TNKase should be given to pregnant women only if the potential benefits justify the potential risk to the fetus.

8.2 Lactation

It is not known if TNKase is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when TNKase is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of TNKase in pediatric patients have not been established.

8.5 Geriatric Use

In the ASSENT-2 study 41% (3500/8458) of patients who were treated with TNKase were aged 65 years or older. In this population rates of 30-day mortality, stroke, intracranial hemorrhage and major bleeds requiring blood transfusion or leading to hemodynamic complications were higher than in those aged less than 65 years. Therefore, in patients aged 65 years and older careful consideration to benefit-risk of treatment with TNKase is recommended.

11 DESCRIPTION

TNKase® is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese Hamster Ovary cells). Tenecteplase is a 527 amino acid glycoprotein developed by introducing the following modifications to the complementary DNA (cDNA) for natural human tPA: a substitution

of threonine 103 with asparagine, and a substitution of asparagine 117 with glutamine, both within the kringle 1 domain, and a tetra-alanine substitution at amino acids 296–299 in the protease domain. TNKase is a sterile, white to pale yellow, lyophilized powder for single intravenous (IV) bolus administration after reconstitution with Sterile Water for Injection (SWFI), USP. Each vial of TNKase nominally contains 52.5 mg tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, which includes a 5% overfill. Each vial will deliver 50 mg of tenecteplase.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tenecteplase is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. In the presence of fibrin, in vitro studies demonstrate that tenecteplase-mediated conversion of plasminogen to plasmin is increased relative to its conversion in the absence of fibrin. This fibrin specificity decreases systemic activation of plasminogen and the resulting degradation of circulating fibrinogen as compared to a molecule lacking this property. The clinical significance of fibrin-specificity on safety (e.g., bleeding) or efficacy has not been established. Biological potency is determined by an in vitro clot lysis assay and is expressed in tenecteplase specific units. The specific activity of tenecteplase has been defined as 200 units/mg.

12.2 Pharmacodynamics

Following administration of 30, 40, or 50 mg of TNKase, there are decreases in circulating fibrinogen (4%–15%) and plasminogen (11%–24%) [TIMI 10A and TIMI 10B].

12.3 Pharmacokinetics

In patients with acute myocardial infarction (AMI), TNKase administered as a single bolus exhibits a biphasic disposition from the plasma. Tenecteplase was cleared from the plasma with an initial half life of 20 to 24 minutes. The terminal phase half-life of tenecteplase was 90 to 130 minutes. In 99 of 104 patients treated with TNKase, mean plasma clearance ranged from 99 to 119 mL/min.

The initial volume of distribution is weight related and approximates plasma volume. Liver metabolism is the major clearance mechanism for tenecteplase.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential, mutagenicity, or the effect on fertility.

14 CLINICAL STUDIES

14.1 Acute Myocardial Infarction

ASSENT-2

ASSENT-2 was an international, randomized, double-blind trial that compared 30-day mortality rates in 16,949 patients assigned to receive an IV bolus dose of TNKase or an accelerated infusion of Activase® (Alteplase).[1] Eligibility criteria included onset of chest pain within 6 hours of randomization and ST-segment elevation or left bundle branch block on electrocardiogram (ECG). Patients were to be excluded from the trial if they received GP IIb/IIIa inhibitors within the previous 12 hours. TNKase was dosed using actual or estimated weight in a weight-tiered fashion as described in *Dosage and Administration (2.1)*. All patients were to receive 150–325 mg of aspirin administered as soon as possible, followed by 150–325 mg daily. Intravenous heparin was to be administered as soon as possible: for patients weighing ≤ 67 kg, heparin was administered as a 4000 unit IV bolus followed by infusion at 800 U/hr; for patients weighing > 67 kg, heparin was administered as a 5000 unit IV bolus followed by infusion at 1000 U/hr. Heparin was continued for 48 to 72 hours with infusion adjusted to maintain aPTT at 50–75 seconds. The use of GP IIb/IIIa inhibitors was discouraged for the first 24 hours following randomization. The results of the primary endpoint (30-day mortality rates with non-parametric adjustment for the covariates of age, Killip class, heart rate, systolic blood pressure and infarct location) along with selected other 30-day endpoints are shown in Table 3.

Table 3 ASSENT-2 Mortality, Stroke, and Combined Outcome of Death or Stroke Measured at Thirty Days

30-Day Events	TNKase (n = 8461)	Accelerated Activase (n = 8488)	Relative Risk TNKase/Activase (95% CI)
Mortality	6.2%	6.2%	1.00 (0.89, 1.12)
Intracranial Hemorrhage (ICH)	0.9%	0.9%	0.99 (0.73, 1.35)
Any Stroke	1.8%	1.7%	1.07 (0.86, 1.35)
Death or Nonfatal Stroke	7.1%	7.0%	1.01 (0.91, 1.13)

Rates of mortality and the combined endpoint of death or stroke among pre-specified subgroups, including age, gender, time to treatment, infarct location, and history of previous myocardial infarction, demonstrate consistent relative risks across these subgroups. There was insufficient enrollment of non-Caucasian patients to draw any conclusions regarding relative efficacy in racial subsets.

Rates of in-hospital procedures, including percutaneous transluminal coronary angioplasty (PTCA), stent placement, intra-aortic balloon pump (IABP) use, and coronary artery bypass graft (CABG) surgery, were similar between the TNKase and Activase® (Alteplase) groups.

TIMI-10B

TIMI 10B was an open-label, controlled, randomized, dose-ranging, angiography study which utilized a blinded core laboratory for review of coronary arteriograms.[2] Patients (n = 837) presenting within 12 hours of symptom onset were treated with fixed doses of 30, 40, or 50 mg of TNKase or the accelerated infusion of Activase and underwent coronary arteriography at 90 minutes. The primary endpoint was the rate of TIMI Grade 3 flow at 90 minutes. The results showed that the 40 mg and 50 mg doses were similar to accelerated infusion of Activase in restoring patency. TIMI Grade 3 flow and TIMI Grade 2/3 flow at 90 minutes are shown in Table 4. The exact relationship between coronary artery patency and clinical activity has not been established.

Table 4 TIMI 10B Patency Rates TIMI Grade Flow at 90 Minutes

	Activase ≤100 mg (n=311)	**TNKase 30 mg (n=302)**	**TNKase 40 mg (n=148)**	**TNKase 50 mg (n=76)**
TIMI Grade 3 Flow	62.7%	54.3%	62.8%	65.8%
(95% CI)	(57.1%, 68.1%)	(48.5%, 60.0%)	(54.5%, 70.6%)	(54.0%, 76.3%)
TIMI Grade 2/3 Flow	81.7%	76.8%	79.1%	88.2%
(95% CI)	(76.9%, 85.8%)	(71.6%, 81.5%)	(71.6%, 85.3%)	(78.7%, 94.4%)

The angiographic results from TIMI 10B and the safety data from ASSENT-1, an additional uncontrolled safety study of 3,235 TNKase-treated patients, provided the framework to develop a weight-tiered TNKase dose regimen.[3] Exploratory analyses suggested that a weight-adjusted dose of 0.5 mg/kg to 0.6 mg/kg of TNKase resulted in a better patency to bleeding relationship than fixed doses of TNKase across a broad range of patient weights.

ASSENT 4 PCI

The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT 4 PCI) was a Phase IIIb/IV study designed to assess the safety and effectiveness of a strategy of administering full dose TNKase with a single bolus of 4000 U of unfractionated heparin in patients with ST segment elevation AMI, in whom primary percutaneous coronary intervention (PCI) was planned, but in whom a delay of 1-3 hours was anticipated before PCI. The trial was prematurely terminated with 1667 randomized patients (75 of whom were in the United States) due to a numerically higher mortality in the patients receiving TNKase prior to primary PCI versus PCI without TNKase (median time from randomization to balloon was 115 minutes in patients who were treated with TNKase plus PCI versus 107 minutes in patients who were treated with PCI alone). The incidence of the 90-day primary endpoint, a composite of death or cardiogenic shock or congestive heart failure (CHF) within 90 days, was 18.6% in patients treated with TNKase plus PCI versus 13.4% in those treated with PCI alone ($p = 0.0045$; RR 1.39 (95% CI 1.11–1.74)).

There were trends toward worse outcomes in the individual components of the primary

endpoint between TNKase plus PCI versus PCI alone (mortality 6.7% vs. 4.9%, respectively; cardiogenic shock 6.3% vs. 4.8%, respectively; and CHF 12.0% vs. 9.2%, respectively). In addition, there were trends towards worse outcomes in recurrent MI (6.1% vs. 3.7%, respectively; p = 0.03) and repeat target vessel revascularization (6.6% vs. 3.4%, respectively; p = 0.004) in patients receiving TNKase plus PCI versus PCI alone.

There was no difference in in-hospital major bleeding between the two groups (5.6% vs. 4.4% for TNKase plus PCI vs. PCI alone, respectively). For patients treated with TNKase plus PCI, in-hospital rates of intracranial hemorrhage and total stroke were similar to those observed in previous trials (0.97% and 1.8%, respectively); however, none of the patients treated with PCI alone experienced a stroke (ischemic, hemorrhagic or other).

15 REFERENCES

1. ASSENT-2 Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716–22.
2. Cannon CP, Gibson CM, McCabe CH, Adgey AAJ, Schweiger MJ, Sequeira RF, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction. Results of the TIMI 10B trial. *Circulation* 1998;98:2805–14.
3. Van de Werf F, Cannon CP, Luyten A, Houbracken K, McCabe CH, Berioli S, et al. Safety assessment of a single bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. *Am Heart J* 1999;137:786–91.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TNKase® is supplied as a sterile, lyophilized powder in a 50 mg vial under partial vacuum.

Each 50 mg vial of TNKase is packaged with one 10 mL vial of Sterile Water for Injection, USP for reconstitution, and the B-D® 10 mL syringe with TwinPak™ Dual Cannula Device: NDC 50242-120-47.

16.2 Stability and Storage

Store lyophilized TNKase at controlled room temperature not to exceed 30°C (86°F) or under refrigeration 2–8°C (36–46°F). Do not use beyond the expiration date stamped on the vial.

17 PATIENT COUNSELING INFORMATION

Following TNKase administration, patients are at increased risk of bleeding internally or externally.

TNKase® (tenecteplase)

Manufactured by:
Genentech, Inc.

A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

U.S. License No. 1048

Representative sample of labeling (see the HOW SUPPLIED section for complete listing):

PRINCIPAL DISPLAY PANEL - 50 mg Kit Carton

NDC 50242-120-01
Tenecteplase
TNKase®
50 mg
Rx only

Kit Contents: Each kit contains one 50 mg vial of TNKase, one 10 mL vial of preservative-free
Sterile Water for Injection, USP, one BD® 10 mL syringe with TwinPak™ Dual Cannula Device,
three alcohol prep pads, and package insert containing full prescribing information.

Vial Contents: The preservative-free single-use vial of TNKase contains 52.5 mg Tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, under partial vacuum. No U.S. standard of potency.

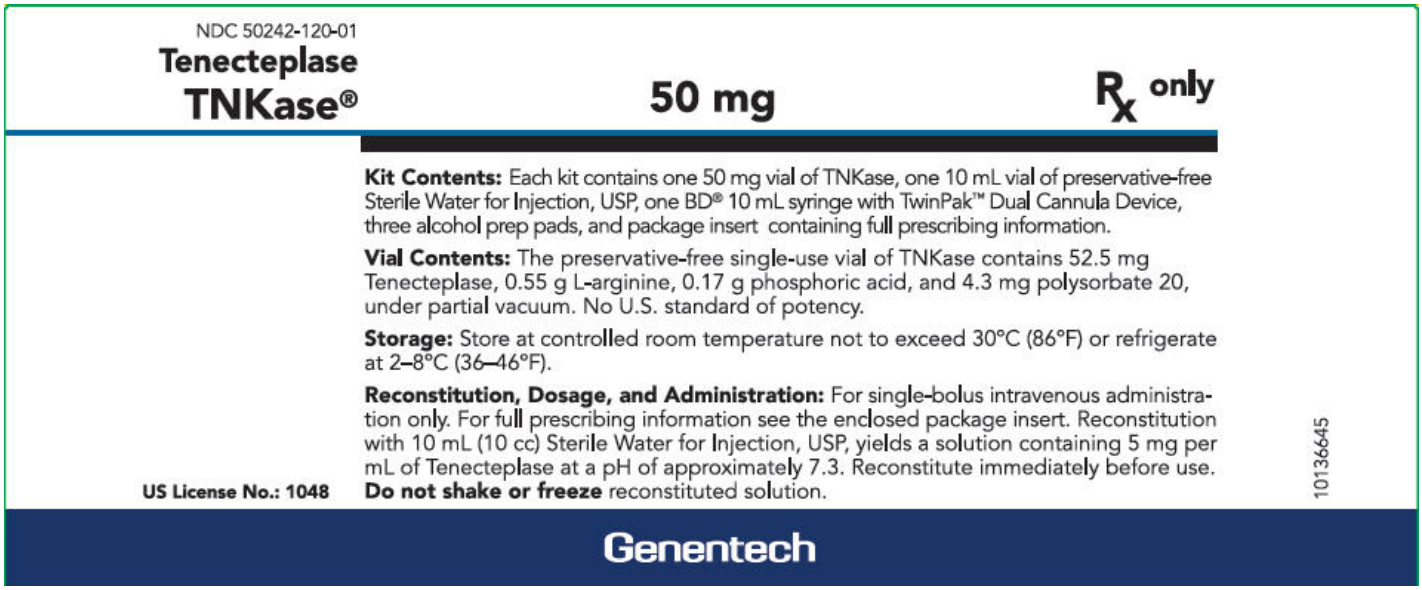
Storage: Store at controlled room temperature not to exceed 30°C (86°F) or refrigerate at 2–8°C (36–46°F).

Reconstitution, Dosage, and Administration: For single-bolus intravenous administration
only. For full prescribing information see the enclosed package insert. Reconstitution with 10 mL (10 cc) Sterile Water for Injection, USP, yields a solution containing 5 mg per mL of Tenecteplase at a pH of approximately 7.3. Reconstitute immediately before use. **Do not shake or freeze** reconstituted solution.

US License No.: 1048

Genentech

10136645



TNKASE

tenecteplase kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50242-120

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:50242-120-01	1 in 1 CARTON	06/02/2000	09/30/2020

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL, SINGLE-USE	50 mg
Part 2	1 VIAL, SINGLE-USE	10 mL
Part 3	1 PACKET	1 mL

Part 1 of 3

TNKASE

tenecteplase injection, solution

Product Information	
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TENECTEPLASE (UNII: WGD229O42W) (TENECTEPLASE - UNII:WGD229O42W)	TENECTEPLASE	52.5 mg in 50 mg

Inactive Ingredients

Ingredient Name	Strength
ARGININE (UNII: 94ZLA3W45F)	0.55 g in 50 mg
PHOSPHORIC ACID (UNII: E4GA8884NN)	0.17 g in 50 mg
POLYSORBATE 20 (UNII: 7T1F30V5YH)	4.3 mg in 50 mg

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		50 mg in 1 VIAL, SINGLE-USE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103909	06/02/2000	09/30/2020

Part 2 of 3

STERILE WATER

water injection

Product Information

Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		10 mL in 1 VIAL, SINGLE-USE; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103909	06/02/2000	09/30/2020

Part 3 of 3

ALCOHOL PREP PADS

isopropyl alcohol swab

Product Information

Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302) (ISOPROPYL ALCOHOL - UNII:ND2M416302)	ISOPROPYL ALCOHOL	0.7 mL in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 mL in 1 PACKET; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103909	06/02/2000	09/30/2020

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103909	06/02/2000	09/30/2020

Labeler - Genentech, Inc. (080129000)

Establishment

Name	Address	ID/FEI	Business Operations
Genentech, Inc.		080129000	ANALYSIS(50242-120) , MANUFACTURE(50242-120) , API MANUFACTURE(50242-120) , PACK(50242-120) , LABEL(50242-120)

Establishment

Name	Address	ID/FEI	Business Operations
Genentech, Inc. (Hillsboro)		833220176	LABEL(50242-120) , PACK(50242-120)

Establishment

Name	Address	ID/FEI	Business Operations
Roche Diagnostics GmbH Pharma Biotech		323105205	ANALYSIS(50242-120)

Establishment

Name	Address	ID/FEI	Business Operations
Genentech, Inc. (OCN)		146373191	ANALYSIS(50242-120)

Establishment

Name	Address	ID/FEI	Business Operations
Roche Singapore Technical Operations Pte. Ltd.		937189173	ANALYSIS(50242-120)

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