

## PRODUCT MONOGRAPH

**PrTNKase<sup>®</sup>**

Tenecteplase

Powder for Solution - 50 mg/Vial  
Sterile, Lyophilized

Fibrinolytic Agent

Distributed by:  
Hoffmann-La Roche Limited  
2455 Meadowpine Boulevard  
Mississauga, Ontario  
L5N 6L7

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

Submission Control No: 120211

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# PrTNKase<sup>®</sup>

Tenecteplase

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
IV bolus	Powder for solution sterile, lyophilized 50 mg/ vial	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

TNKase (tenecteplase) is indicated for intravenous use in adults for the lysis of suspected occlusive coronary artery thrombi associated with evolving transmural myocardial infarction to reduce the mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms.

The ASSENT-2 clinical trial compared single bolus weight adjusted TNKase with accelerated Activase<sup>®</sup> (rt-PA) (alteplase) in patients presenting within 6 hours of onset of AMI symptoms (see CLINICAL TRIALS).

**Geriatrics:** For clinical use in geriatric patients please refer to WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics.

### CONTRAINDICATIONS

Therapy with TNKase (tenecteplase) in patients with acute myocardial infarction is contraindicated in the following situations because of an increased risk of bleeding (see WARNINGS AND PRECAUTIONS):

- 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
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

## **WARNINGS AND PRECAUTIONS**

### **General**

Each patient being considered for therapy with TNKase (tenecteplase) should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risk of therapy with TNKase 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  $\geq$  180 mm Hg and/or diastolic BP  $\geq$  110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- 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 WARNINGS AND PRECAUTIONS: Geriatrics)
- 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

Standard management of myocardial infarction should be implemented concomitantly with TNKase treatment. Arterial and venous punctures should be minimized. Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the noncompressible sites. In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately. Heparin effects can be reversed by protamine.

All plasminogen activators, including TNKase, should be used in conjunction with anticoagulants. There are some patients that may require further intervention to achieve reperfusion. Adherence to the ACC/AHA anticoagulation guidelines is recommended.

## **Bleeding**

The most common complication encountered during therapy with TNKase is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or sites of recent surgical intervention.

Should serious bleeding (not controlled by local pressure) occur, any concomitant heparin and antiplatelet agents should be discontinued immediately.

In clinical studies of TNKase, patients were treated with both ASA and heparin. Heparin may contribute to the bleeding risks associated with TNKase. The safety of the use of TNKase with other antiplatelet agents has not been adequately studied (see DRUG INTERACTIONS). Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with TNKase. Venipunctures should be performed and monitored carefully.

Should an arterial puncture be necessary during the first few hours following therapy with TNKase, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

## **Carcinogenesis and Mutagenesis**

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

## **Cardiovascular**

### **Arrhythmias**

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and 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.

### **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.

## **Endocrine and Metabolism**

### **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. Clinical features of cholesterol embolism may include livedo reticularis “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

## **Sensitivity/Resistance**

### **Readministration**

Readministration of plasminogen activators, including TNKase, to patients who have received prior plasminogen activator therapy has not been systematically studied. Three of 487 patients tested for antibody formation to TNKase had a positive antibody titer at 30 days. The data reflect the percentage of patients whose test results were considered positive for antibodies to TNKase in a radioimmunoprecipitation assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, 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. Although sustained antibody formation in patients receiving one dose of TNKase has not been documented, readministration should be undertaken with caution. If an anaphylactic reaction occurs, appropriate therapy should be administered.

## **Special Populations**

*Pregnant Women:* 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 (See TOXICOLOGY).

*Nursing Women:* It is not known if TNKase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TNKase is administered to a nursing woman (See TOXICOLOGY).

*Pediatrics:* Safety and effectiveness of TNKase in pediatric patients have not been established.

*Geriatrics:* In elderly patients, the benefits of TNKase on mortality should be carefully weighed against the risk of increased adverse events, including bleeding (see Table 1).

**Table 1**  
ASSENT-2

Elderly Patients Who Received TNKase

Event Rate	Age		
	< 65 years n = 4958 (59%)	65 - 74 years n = 2256 (27%)	≥ 75 years n = 1244 (15%)
<b>30-Day Mortality</b>	2.5%	8.5%	16.2%
<b>Intracranial Hemorrhage (ICH)</b>	0.4%	1.6%	1.7%
<b>Any Stroke</b>	1.0%	2.9%	3.0%
<b>Major Bleeding*</b>	3.1%	6.4%	7.7%

\*defined as bleeding requiring blood transfusion or leading to hemodynamic compromise

**Monitoring and Laboratory Tests**

During therapy with TNKase, 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.

**ADVERSE REACTIONS**

**Adverse Drug Reaction Overview**

**Bleeding**

The most frequent adverse reaction associated with TNKase (tenecteplase) is bleeding (see WARNINGS AND PRECAUTIONS).

Should serious bleeding occur, concomitant heparin and antiplatelet therapy should be discontinued. Death or permanent disability can occur in patients who experience stroke or serious bleeding episodes.

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

For TNKase treated patients in ASSENT-2, the incidence of intracranial haemorrhage was 0.9% and any stroke was 1.8%. The incidence of all strokes, including intracranial bleeding, increases with increasing age (see WARNINGS AND PRECAUTIONS: Geriatrics).

In the ASSENT-2 study, the following bleeding events were reported (see Table 2)

<b>Table 2</b>				
<b>ASSENT-2</b>				
<b>Non-ICH Bleeding Events</b>				
	TNKase (n = 8461)	Accelerated ACTIVASE (n = 8488)	Relative Risk for TNKase/ACTIVASE (95% CI)	p-value
Major bleeding*	4.7%	5.9%	0.78 (0.69, 0.89)	0.0002
Minor bleeding	21.8%	23.0%	0.94 (0.89, 1.00)	0.0553
Units of transfused blood				
Any	4.3%	5.5%	0.77 (0.67, 0.89)	0.0013
1-2	2.6%	3.2%		
> 2	1.7%	2.2%		
*defined as bleeding requiring blood transfusion or leading to hemodynamic compromise				

The incidence of non-intracranial major bleeding and the need for blood transfusions were statistically lower in patients treated with TNKase compared to an accelerated infusion of ACTIVASE.

Types of major bleeding reported in 1% or more of the patients were hematoma (1.7%) and gastrointestinal tract (1%). Types of major bleeding reported in less than 1% of the patients were urinary tract, puncture site (including cardiac catheterization site), retroperitoneal, respiratory tract, and unspecified. Types of minor bleeding reported in 1% or more of the patients were hematoma (12.3%), urinary tract (3.7%), puncture site (including cardiac catheterization site) (3.6%), pharyngeal (3.1%), gastrointestinal tract (1.9%), epistaxis (1.5%), and unspecified (1.3%).

## Allergic Reactions

Allergic-type reactions (e.g., anaphylaxis, angioedema, laryngeal edema, rash, and urticaria) have rarely (< 1%) been reported in patients treated with TNKase. Anaphylaxis was reported in < 0.1% of patients treated with TNKase; however, causality was not established. When such reactions occur, they usually respond to conventional therapy.

## Other Adverse Reactions

The following serious adverse reactions have been reported among patients receiving TNKase in the ASSENT-2 clinical trial. These reactions are frequent sequelae of the underlying disease, and the effect of TNKase on the incidence of these events is unknown. These events can be life-threatening and may lead to death.

**Table 3**

\*Serious Non-Bleeding Events Reported in  $\geq 1\%$  of Patients in the ASSENT- 2 Trial

	TNKase (n=8258)	Accelerated Activase (n=8299)
<b>Cardiovascular</b>		
Cardiogenic Shock	3%	3%
Hypotension	3%	3%
Electromechanical dissociation	2%	2%
Myocardial reinfarction	2%	2%
Recurrent myocardial ischemia	2%	2%
Atrioventricular block	1%	1%
<b>Respiratory</b>		
Pulmonary edema	2%	3%

\*Reported adverse events are without attribution

Serious non-bleeding events reported in the ASSENT-2 trial at a frequency of <1% include arrhythmias, heart failure, cardiac arrest, myocardial rupture, cardiac tamponade, pericarditis, pericardial effusion, mitral regurgitation, thrombosis, embolism, nausea and/or vomiting, and fever.

## Post-Market Adverse Drug Reactions

Adverse events that have been reported during the post-marketing period are consistent with those seen in clinical trials with TNKase.

## DRUG INTERACTIONS

### Drug Interactions

Formal interaction studies of TNKase (tenecteplase) with other drugs have not been performed. Patients studied in clinical trials of TNKase were routinely treated with heparin and ASA. 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 therapy with TNKase.

## DOSAGE AND ADMINISTRATION

### Dosage

TNKase (tenecteplase) is for intravenous administration only. The recommended total dose should not exceed 50 mg and is based upon patient weight.

A single bolus dose should be administered over 5 seconds based on patient weight. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL TRIALS).

**Dose Information Table**

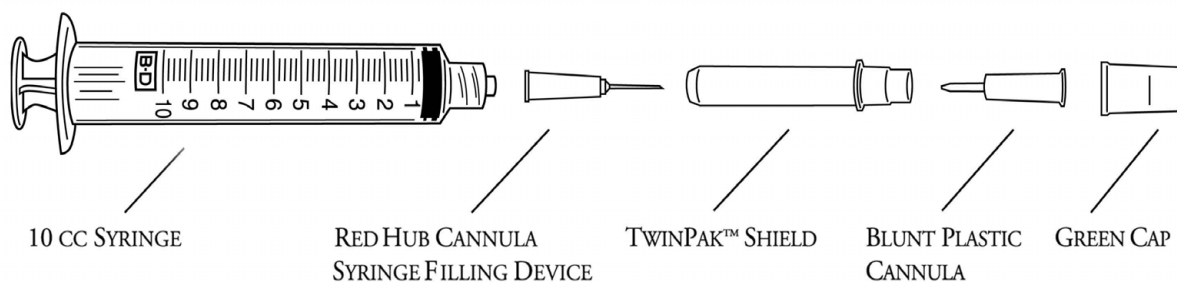
Patient Weight (kg)	TNKase (mg)	Volume TNKase <sup>a</sup> to be administered (mL)
< 60	30	6
≥ 60 to < 70	35	7
≥ 70 to < 80	40	8
≥ 80 to < 90	45	9
≥ 90	50	10

<sup>a</sup> 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 ASA as described in CLINICAL TRIALS.

### Reconstitution

#### The B-D® 10cc Syringe with TwinPak® Dual Cannula Device



**NOTE:** Read all instructions completely before beginning reconstitution and administration

1. Remove the shield assembly from the supplied B-D<sup>®</sup> 10 cc Syringe with TwinPak<sup>®</sup> Dual Cannula Device (see figure) 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.

2. 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.
3. Gently swirl until contents are completely dissolved. **Do not shake.** The reconstituted preparation results in a colourless 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.
4. Determine the appropriate dose of TNKase (see Dose Information Table) and withdraw this volume (in milliliters) from the reconstituted vial with the syringe. Any unused solution should be discarded.
5. 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.
6. Remove the entire shield assembly, including the red hub cannula, by twisting counter-clockwise. Note: The shield assembly also contains the clear-ended blunt plastic cannula; retain for split septum IV access

## Administration

1. The product should be visually inspected prior to administration for particulate matter and discoloration. TNKase may be administered as reconstituted at 5 mg/mL.
2. Precipitation may occur when TNKase is administered in an IV line containing dextrose. Dextrose containing lines should be flushed with a saline containing solution prior to and following single bolus administration of TNKase.
3. Reconstituted TNKase should be administered as a single IV bolus over 5 seconds.
4. Because TNKase contains no antibacterial preservatives, it should be reconstituted immediately before use. If the reconstituted TNKase is not used immediately, refrigerate the TNKase vial at 2 – 8°C and use within 8 hours.

5. 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.

<b>Split septum IV system:</b>	<ul style="list-style-type: none"> <li>• Remove the green cap.</li> <li>• Attach the clear-ended blunt plastic cannula to the syringe.</li> <li>• Remove the shield and use the blunt plastic cannula to access the split septum injection port.</li> <li>• 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.</li> </ul>
<b>Luer-Lok® system:</b>	<ul style="list-style-type: none"> <li>• Connect syringe directly to IV port.</li> </ul>
<b>Conventional needle (not supplied in this kit):</b>	<ul style="list-style-type: none"> <li>• Attach a large bore needle, e.g., 18 gauge, to the syringe's universal Luer-Lok®.</li> </ul>

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

## OVERDOSAGE

Single doses greater than 50 mg (10,000 units) have not been tested. The total dose should be based on patient weight, not to exceed 50 mg (see DOSAGE AND ADMINISTRATION).

Any patients receiving greater than the recommended dosage should be carefully monitored. Bleeding complications, notably Intracranial Hemorrhage (ICH), are the most important adverse events associated with TNKase (tenecteplase), as with other thrombolytics. If bleeding occurs, standard medical management should be implemented.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

TNKase (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 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. Following administration of 30, 40, or 50 mg of TNKase, there are decreases in circulating fibrinogen (4%-15%) and plasminogen (11%-24%). 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 TNKase has been defined as 200 units/mg.

### **Pharmacokinetics**

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

**Distribution:** The initial volume of distribution is weight related and approximates plasma volume.

**Metabolism:** The major route of clearance of TNKase is liver metabolism.

### **STORAGE AND STABILITY**

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

Unused reconstituted TNKase (in the vial) may be stored at 2°C - 8°C and used within 8 hours. After that time, any unused portion of the reconstituted material should be discarded.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

#### **Dosage Forms:**

TNKase (tenecteplase) is supplied as a sterile, lyophilized powder in a 50 mg, glass (20 cc) vial under partial vacuum.

#### **Composition:**

TNKase is a sterile, white to off-white, lyophilized powder for single intravenous (IV) bolus administration after reconstitution with Sterile Water for Injection, USP.

#### **50 mg (10,000 units) / vial**

Tenecteplase\* 52.5 mg

L-Arginine	0.55 g
Phosphoric Acid	0.17 g
Polysorbate 20	4.3 mg

\*This includes a 5% overfill so that each vial will deliver 50 mg of tenecteplase.

#### **Packaging:**

Each 50 mg vial of TNKase is packaged with one 10 mL vial of Sterile Water for Injection, USP for reconstitution, one B-D<sup>®</sup> 10 cc Syringe with TwinPak<sup>®</sup> Dual Cannula Device, and three alcohol prep pads.