PRODUCT MONOGRAPH

PrTNKase®

tenecteplase for injection

Powder for Solution - 50 mg/Vial
Sterile, Lyophilized

Fibrinolytic Agent

Distributed by:
Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario
L5N 5M8

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Table of Contents

PrTNKnase®

tenecteplase for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

TNKase (tenecteplase for injection) 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® (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 for injection) 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 for injection) 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 non-compressible 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
- 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. Non-compressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the non-compressible 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 and appropriate treatment should be considered.

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 non-essential 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.

Thromboembolism

The use of thrombolytics can increase the risk of thrombo-embolic events in patients with left heart thrombus, e.g., mitral stenosis or atrial fibrillation.

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.

Hypersensitivity
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%)**
30-Day Mortality	2.5%	8.5%	16.2%
Intracranial Hemorrhage (ICH)	0.4%	1.6%	1.7%
Any Stroke	1.0%	2.9%	3.0%
Major Bleeding*	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 for injection) 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)

Table 2 ASSENT-2 - Non-ICH Bleeding Events

	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 ≥1% of Patients in the ASSENT- 2 Trial

	TNKase (n=8258)	Accelerated Activase (n=8299)
Cardiovascular		
Cardiogenic Shock	3%	3%
Hypotension	3%	3%
Electromechanical dissociation	2%	2%
Myocardial reinfarction	2%	2%
Recurrent myocardial ischemia	2%	2%
Atrioventricular block	1%	1%
Respiratory		
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 for injection) 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 for injection) 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

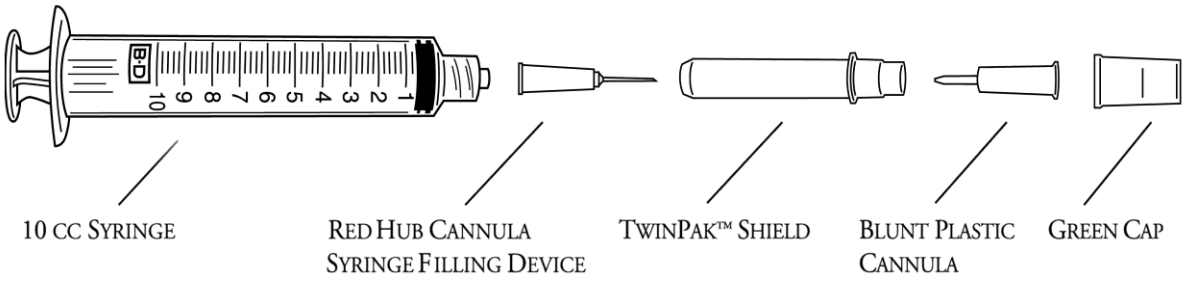
Patient Weight (kg)	TNKase (mg)	Volume TNKase [a] to be administered (mL)
< 60	30	6
≥ 60 to < 70	35	7
≥ 70 to < 80	40	8
≥ 80 to < 90	45	9
≥ 90	50	10

[a] 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® 10 cc Syringe with TwinPak® 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.

Split septum IV system:	• Remove the green cap. • Attach the clear-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®.

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 for injection), as with other thrombolytics. If bleeding occurs, standard medical management should be implemented.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TNKase (tenecteplase for injection) 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 for injection) 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. The composition of the lyophilized product is, tenecteplase (medicinal ingredient), L-arginine, phosphoric acid and polysorbate 20.

Packaging:
Each 50 mg vial of TNKase is packaged with one 10 mL vial of Sterile Water for Injection, USP for reconstitution and one B-D® 10 cc Syringe with TwinPak® Dual Cannula Device.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper Name: Tenecteplase

Drug Substance: Tenecteplase 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.

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.

CLINICAL TRIALS

ASSENT-2 was an international, randomized, double-blind, double-dummy, parallel group trial that compared 30-day mortality rates in 16,949 patients assigned to receive an IV bolus dose of TNKase (tenecteplase for injection) or an accelerated infusion of ACTIVASE. Eligibility criteria included onset of chest pain within 6 hours of randomization and ST-segment elevation or new 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. All patients were to receive 150-325 mg of acetylsalicylic acid (ASA) 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 4. Single-bolus TNKase was equivalent to ACTIVASE in the effect on 30-day mortality.

Table 4

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 Non-fatal 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. In patients assigned treatment after 4 hours, a lower mortality with TNKase was observed. 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 group treated with TNKase and group treated with ACTIVASE.

TIMI 10B was an open-label, controlled, randomized, dose-ranging, angiography study which utilized a blinded core laboratory for review of coronary arteriograms. 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 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 5. The exact relationship between coronary artery patency and clinical activity has not been established.

Table 5
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	63%	54%	63%	66%
TIMI Grade 2/3 Flow	82%	77%	79%	88%
95% CI (TIMI 2/3 Flow)	(77%,86%)	(72%,81%)	(72%,85%)	(79%,94%)

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. 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.

In elderly patients, the benefits of TNKase on mortality should be carefully weighed against the risk of increased adverse events, including bleeding (see WARNINGS AND PRECAUTIONS, Geriatrics).

DETAILED PHARMACOLOGY

Non-clinical Pharmacology

In vitro, TNKase (tenecteplase for injection) exhibits plasma clot lysis activity similar to ACTIVASE, but it is approximately 10- to 14-fold more fibrin specific, and is more resistant to inhibition by plasminogen activator inhibitor type I (PAI-1). When added to human plasma, TNKase consumes less fibrinogen on a mass basis than does ACTIVASE.

Rabbits are the species most studied because they appear to be the most relevant for prediction of fibrinolytic properties of thrombolytics in humans. In a rabbit model of clot lysis (AV shunt), TNKase was found to be approximately 3 to 7 times as potent in lysing whole blood clots compared to Alteplase (ACTIVASE and Actilyse®).

In a rabbit model of embolic stroke, TNKase was about 5- to 10-fold more potent than ACTIVASE. Specifically, an IV bolus dose of 0.6 mg/kg TNKase was comparable in clot lysis to an ACTIVASE dose of 3.0 mg/kg infused over one hour.

In a rabbit model of electrically-induced carotid artery thrombosis, bolus doses of 1.5 mg/kg TNKase compared favourably with infusions of 9.0 mg/kg ACTIVASE. This model of thrombolytic potency has shown TNKase to be superior to ACTIVASE with respect to incidence of reperfusion, duration of patency, and extent of lysis.

In a canine model of electrically-induced coronary artery thrombosis, 1 mg/kg doses of TNKase given as an IV bolus and ACTIVASE given as an IV infusion were equally effective. However, TNKase demonstrated a higher incidence of patency, lower rate of reocclusion, and greater duration of patency compared to ACTIVASE.

TOXICOLOGY

Summary

Toxicology studies performed with TNKase (tenecteplase for injection) support bolus intravenous administration to humans. Acute and subacute toxicity studies were conducted in the rat, dog, and rabbit. The rat and dog have been used for safety studies of thrombolytics, including ACTIVASE, and the toxicology program was based on the extensive historical data generated in these species. In addition, the potential for interaction when TNKase is coadministered with acetyl salicylic acid and heparin was evaluated in the acute dog study.

No unexpected toxicities were produced by TNKase following a single administration up to 50 mg/kg in rats and 30 mg/kg in rabbits and dogs. The high dose used in the rabbit and dog studies provides a minimum safety factor of approximately 57-fold (based on body weight) over the expected clinical dose (approximately 0.53 mg/kg). The observed effects of TNKase on blood coagulation were expected given the known pharmacology of this class of drug. TNKase was antigenic in rabbits and dogs after a single administration; dogs given a challenge dose two weeks after the initial dose showed severe signs of anaphylaxis followed by death at a dose level of 30 mg/kg. This is not an unexpected response following administration of a heterologous protein. Additionally, the presence of arginine in the vehicle was also associated with angioedema in dogs, but the effect seems to be species specific since there was no evidence of angioedema in rats or rabbits and given that there is no evidence of angioedema associated with ACTIVASE vehicle administration in humans. Coadministration of acetyl salicylic acid and heparin with TNKase did not potentiate the effect of TNKase on indices of blood coagulation or cause any additional toxicity.

Daily administration of TNKase to rats for 15 days at doses up to 10 mg/kg was well tolerated. Administration of up to 3 mg/kg of TNKase to rats had no effect on clinical pathology

parameters. As expected, rats dosed with TNKase developed antibody titers to TNKase by Day 16.

A direct comparison of the toxicity of TNKase versus ACTIVASE was performed in a multidose dog study. Daily administration of TNKase at doses up to 10 mg/kg for at least 8 days, or daily 90-minute infusions of ACTIVASE for 14 days, were well tolerated and produced pharmacologically expected effects on the blood coagulation system. Treatment with TNKase elicited an immune response consistent with anaphylaxis in dogs, at 1 mg/kg or higher, by the ninth day of treatment, which included development of antibodies to TNKase. In animals given ACTIVASE the anaphylactic response was present but less severe. Antibody titers to ACTIVASE were observed by Day 14. These findings are expected following the administration of a heterologous protein. As in the acute dog study, all treatments caused angioedema due to the presence of arginine in the vehicles.

Cardiovascular, respiratory, renal, and behavioural safety pharmacology studies were conducted to characterize the toxicity of TNKase on these organ systems. TNKase had no effect on these organ systems at doses up to 3 mg/kg.

A series of developmental toxicity studies were conducted to assess the effects of TNKase on the pregnant rabbit and its developing fetus. 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, 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 was 5 mg/kg (approximately 8-10 times the human dose). No toxicity was observed, following a single administration of TNKase during the period of organogenesis in the rabbit. However, multiple administrations of TNKase induced embryo and maternal toxicity and death from gestation Days 13 to 17 in the rabbit.

The tables presented on the following pages provide the findings of the main toxicology, reproductive, and various special studies performed with tenecteplase.

Table-6 Acute Toxicity Studies

Study No.	Study Type	Species/ Strain	No./ Sex/ Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a]	Tenecteplase Lot No.	Study Duration	Study Location
						Body Weight Ratio			
94-086-0218 (Covance 6281-318)	Rat Acute Single Dose (GLP)	Rat/Crl:CD® (SD) BR VAF/Plus	5/M 5/F	IV (bolus)	0	–	M4-RD312	2 weeks	Covance
					0.5	0.79			
					5.0[b]	7.9			
					50.0	79			
Comments: No test material-related clinical signs of toxicity were observed. Tenecteplase at a single dose up to and including 50 mg/kg was well tolerated and produced no evidence of toxicity.									
94-092-0218 (Covance 6281-323)	Rabbit Acute Single Dose (GLP)	Rabbit Hra:(NZW) SPF	5/M 5/F	IV (bolus)	0	–	M4-RD312	2 weeks	Covance
					0.3	0.48			
					3.0	4.8			
					30.0	48			
Comments: A single dose of tenecteplase was well tolerated and produced no evidence of toxicity at doses up to and including 30 mg/kg. Administration of tenecteplase produced expected pharmacological effects on the blood coagulation system that were demonstrated by clinical pathology evaluations. By Day 14, animals treated with tenecteplase had developed antibodies to tenecteplase in a dose-dependent manner.									

Table 6 Acute Toxicity Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./Sex /Group	Route of Admin.	Group	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Tenecteplase Lot No.	Study Duration	Study Location
94-090-0218 (Covance 6281-322)	Beagle Dog Acute Single Dose w/ Challenge Dose on Day 14 (GLP)	Canine/ Beagle	2/M 2/F	IV (bolus)	1	0	–	M4-RD312	3 weeks	Covance
					2	0.3	0.48			
					3	3.0	4.8			
					4	30.0	48			
					5	0 + ASA + Heparin[c]	–			
					6	0.3 + ASA + Heparin[c]	0.48			
					7	3.0 + ASA + Heparin[c]	4.8			
					8	30.0 + ASA + Heparin[c]	48			

Comments: A single intravenous injection of tenecteplase up to and including 30 mg/kg was well tolerated and produced expected pharmacological effects on the blood coagulation system. Coadministration of tenecteplase with ASA and heparin did not appear to potentiate the effects of tenecteplase.Tenecteplase produced no effects on body weights, cumulative body weight gains, or food consumption. Tenecteplase and tenecteplase Vehicle caused angioedema which may have been due to the presence of arginine in the vehicle. Administration of tenecteplase produced a dose-dependent antigenic response. High antibody titers correlated with signs of anaphylactic shock followed by death in the high dose (30 mg/kg) animals receiving a challenge dose on Day 14. This is not an unexpected response following administration of a heterologous protein.

[a] Estimated Safety Factor's were obtained by calculating the ratio of either dose, plasma exposure, or peak concentration in each species to the corresponding value for humans in the Phase II clinical trial.

[b] Based on dose analysis results, it was determined that these animals were dosed at 10 mg/kg.

[c] To evaluate possible interaction effects of commonly used thrombolytic adjuncts, animals in Groups 5–8 received 162.5 mg of acetylsalicylic acid (ASA) orally, approximately 24 and 2 hours before administration of tenecteplase or tenecteplase Vehicle. Immediately following administration of tenecteplase or tenecteplase Vehicle, these animals received an IV injection of heparin (100 unit/kg; 2 mL/kg), followed by an approximate 4-hour intravenous infusion of heparin (50 units/kg/hour; 1 mL/hour).

Table 7 Subacute Toxicity Studies

Study No.	Study Type	Species/ Strain	No./ Sex/ Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a]	Tenecteplase Lot No.	Study Duration	Study Location
						Body Weight Ratio			
94-087-0218 (Covance 6281-317)	Rat Multidose (GLP)	Rat/Crl:CD® (SD) BR VAF/Plus	10-15/M 10-15/F	IV (bolus; daily)	0	–	M4-RD312	4 weeks	Covance
					0.3	0.5			
					1.0	1.6			
					3.0	5.0			
					10.0	16			

Comments: Daily bolus intravenous injections of tenecteplase for up to 2 weeks was well tolerated and produced no observable adverse effects at doses up to and including 10 mg/kg. By Day 16, animals treated with tenecteplase had developed antibodies to tenecteplase in a dose-dependent manner.

Table 7 Subacute Toxicity Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Tenecteplase Lot No.	Study Duration	Study Location
94-091-0218 (Covance 6281-321)	Beagle Dog Multidose (GLP)	Canine/ Beagle	4–6/ M 4–6/F	Tenecteplase IV (bolus; daily)	0	–	M4-RD313 (Tenecteplase)	4 weeks	Covance
					0.3	0.48			
					1.0	1.6			
					3.0	4.8			
					10.0	16			
				ACTIVASE (90-minute infusion; daily)	0	–	Y9509AX (ACTIVASE)		
					10.0 (ACTIVASE)	4.8[b]			

Comments: Daily bolus IV doses of 0.3 mg/kg of tenecteplase for at least 9 days were well tolerated and produce no evidence of toxicity in dogs. Higher doses (1, 3, or 10 mg/kg) of tenecteplase and (10 mg/kg) ACTIVASE produced the expected exaggerated pharmacological effects on blood coagulation parameters in a dose-related manner. Multiple administration of tenecteplase at dose levels of 1 mg/kg or higher, produced a greater incidence and severity of perivascular hemorrhage in the liver and hemorrhage around gallbladder and in the lymph nodes, compared to animals given tenecteplase Vehicle or 0.3 mg/kg tenecteplase. These latter findings are consistent with the expected pharmacological action of tenecteplase in tissues following trauma caused by vascular damage as a result of animal handling. A decreased incidence and severity of these findings in animals treated with ACTIVASE was attributed to the difference in the exposure and administration procedure. Animals developed antibodies in dose-dependent manner to tenecteplase and ACTIVASE. All treatments caused angioedema which may have been due to the presence of arginine in the vehicles. Tenecteplase elicited a dose-related immune response consistent with anaphylaxis in animals given 1 mg/kg or higher; in animals given ACTIVASE the response was present, but less severe. This is not an unexpected response following administration of a heterologous protein.

[a] Estimated Safety Factor's were obtained by calculating the ratio of either dose, plasma exposure, or peak concentration in each species to the corresponding value for humans in the Phase II clinical trial.

[b] Based on an ACTIVASE dose in a human of 2.1 mg/kg.

Table 8 Special Toxicity Studies

Study No.	Study Type	Species/ Strain	No./ Sex/ Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a]		Lot No.	Study Duration	Study Location
						Body Weight Ratio				
94-088-0218 (Covance 6281-319)	*In Vitro* Hemolysis and Blood Compatibility (GLP)	Human and Beagle Dog	NA	NA	0, 5 mg/mL	NA	NA	M4-RD312	25–45 minutes	Covance
Comments: No hemolysis or incompatibility was observed for tenecteplase at a concentration of 5 mg/mL or tenecteplase Vehicle when mixed with equal volumes of beagle dog and human blood, serum, or plasma.										
94-089-0218 (Covance 6281-320)	Acute IV Local Tolerance (GLP)	Rabbit Hra: (NZW) SPF	9/M	IV (Bolus)	0, 5 mg/mL	NA	NA	M4-RD312	1 week	Covance
Comments: Local redness and swelling associated with administration of the test material may have been associated with mechanical aspects of the injection process and exacerbated by the pharmacological activity of tenecteplase. No clinical observations or histopathological findings indicative of local irritation were attributed to tenecteplase.										

Table 8 Special Toxicity Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Lot No.	Study Duration	Study Location
93-539-0210 (Covance 6281-320)	Beagle Dog Pilot Multidose (non-GLP)	Canine/ Beagle	2/M, 2/F	ACTIVASE (IV infusion)	0	–	Y9509AX	2 weeks	Covance
					3	1.4[b]			
					10	4.8[b]			
					30	14.2[b]			
				Saline	0	–			

Comments: Administration of ACTIVASE to dogs by daily intravenous for at least 7 days (30 mg/kg) or 14 days (3 or 10 mg/kg) produced expected pharmacological effects on the blood coagulation system that were demonstrated by clinical pathology evaluations and increased bleeding from venipuncture sites. Increases in plasma histamine levels induced by ACTIVASE on Day 9 were likely secondary to an antigenic response to the test material since all animals that received ACTIVASE were positive for anti-–ACTIVASE antibodies. On Days 8 and 9, dosing was stopped prior to completion for animals in the 30 mg/kg dose group due to severe signs of apparent hypotension. In general, within 2–8 minutes after initiation of dosing, animals became uncoordinated or unable to stand. Excessive salivation and pale mucous membranes were usually observed. The reduction in blood pressure observed in animals in the 30 mg/kg dose group may have been related to the increased histamine levels.

Table 8 Special Toxicity Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Lot No.	Study Duration	Study Location
96-361-0366 (Genentech)	Rabbit Multidose (non-GLP)	Rabbit Hra: (NZW) SPF	3/F	IV	0	–	D9821AX	3 weeks	Genentech
					1	1.6			
					3	4.8			
					10	16			
Comments: Daily administration of tenecteplase produced an antibody response in all treated animals by Study Day 8. Animals treated with tenecteplase, regardless of the dose level, bled at the injection catheter following treatment with tenecteplase. The bleeding is an expected pharmacological effect of tenecteplase, a thrombolytic agent. In latter days of treatment with tenecteplase (Days 9–13), the bleeding was less profound. This altering of the pharmacological effect coincided with the formation of antibodies to tenecteplase. Based on the results of this study for use in designing future studies; production of anti-tenecteplase antibodies will most likely confound pharmacokinetic and pharmacodynamic evaluations of tenecteplase if animals are dosed daily for 7 or more days.									
97-066-0218 (HLS GET1)	Monkey Cardio-vascular Safety-Pharm. (GLP)	Cynomolgus Monkey	3/F	IV	0	–	M3-RD622	10 days	HLS
					0.003	0.0048			
					0.03	0.048			
					0.3	0.48			
					3	4.8			
					30	48			
Comments: Bolus IV administration of tenecteplase was well tolerated and did not adversely affect the cardiovascular parameters evaluated in this safety pharmacology study at dose up to and including 3.0 mg/kg in cynomolgus monkeys. Bolus IV administration of tenecteplase at a dose of 30 mg/kg (approximately 57x the intended clinical dose) produced ataxia, hypotension, alteration of ECG T-wave, and bleeding at previous venipuncture sites in the animals. These observations are the expected exaggerated pharmacological effect produced by a thrombolytic at this high dose.									

Table 8 Special Toxicity Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Lot No.	Study Duration	Study Location
98-302-0218 (BI U95-2113)	Rabbit Cardio-vascular/ Respiratory Safety-Pharm. (non-GLP)	Rabbit: NZW	3/M, 3/F	IV	0	–	B9813AX/ G124G	3 hours	Boehringer Ingeheim
					0.03	0.048			
					0.1	0.16			
					0.3	0.48			
					1	1.6			
					3	4.8			
Comments: A single IV administration of tenecteplase, up to 3 mg/kg, had no acute effect (30 minutes postdose evaluations) on respiratory and cardiovascular function in rabbits.									
98-303-0218 (BI U95-2122)	Mouse General Pharm. (Behavior) (non-GLP)	SPF-mice	5/M, 5/F	IV	0	–	B9813AX/ G124G	24 hours	Boehringer Ingeheim
					1	1.6			
					3	4.9			
					10	16			
Comments: Behavior in mice was generally not affected by IV administration of tenecteplase (1, 3, and 10 mg/kg). A dose-dependent loss of grasping and landing reflex was observed, which appeared not to be due to muscle relaxation. A preference of staying in the center of the cage as well as a slight increase in body temperature were recorded in the 3 mg/kg dose group.									

Table 8 Special Toxicity Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Lot No.	Study Duration	Study Location
98-306-0218 (BI U98-2718)	Dog Safety/ Parm. (Renal) (non-GLP)	Beagle dog	8/F	IV	0 1 3 9	– 1.6 4.8 14	NF6529AM04	1 week	Boehringer Ingeheim
Comments: Tenecteplase (1-9 mg/kg) administered intravenously, had no major effect on renal function in conscious dogs. Adverse effects observed following administration of tenecteplase Vehicle and all dose levels of tenecteplase were related to a dog-specific intolerability to arginine in the tenecteplase Vehicle.									
98-304-0218 (BI U98-2566)	Acute IA Local Tolerance (GLP)	Rabbit: Chbb:NZW	2/M, 2/F	IA	0, 5 mg/mL	NA	NF 6532 AM01/3	11 days	Boehringer Ingeheim
Comments: Intra-arterial administration of tenecteplase (5 mg/mL) into the right and left A. auricularis of rabbits was well tolerated. Hematomas observed at the injection site in the tenecteplase-treated rabbits were most likely associated with the mechanical aspects of the injection process and exacerbated by the pharmacological activity of tenecteplase.									
98-305-0218 (BI U98-2567)	Acute PV Local Tolerance (GLP)	Rat: Chbb: THOM (SPF)	4/M, 4/F	PV	0, 5 mg/mL	NA	NF 6532 AM01/3	24 hours	Boehringer Ingeheim
Comments: Tenecteplase (5mg/mL) was found to be well tolerated after a single paravenous injection in rats. Slight hemorrhaging in the paravenous area was observed in 3 of 4 females treated with tenecteplase. This finding is not regarded to be an irritation symptom, but is most likely associated with the mechanical aspects of the injection process and exacerbated by the pharmacological activity of tenecteplase. This finding was not noted for the remaining (1 female and 4 males) tenecteplase treated animals.									

[a] Estimated Safety Factor's were obtained by calculating the ratio of either dose, plasma exposure, or peak concentration in each species to the corresponding value for humans in the Phase II clinical trial.

[b] Based on an ACTIVASE dose in a human of 2.1 mg/kg.

Table 9 Developmental Reproductive Studies

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Lot No.	Study Duration	Study Location
96-440-0218 (Argus 107-012)	Pregnant Rabbit Developmental Study (GLP)	Rabbit Hra: (NZW) SPF	18/F	IV	0	–	D9821AX	1 month	Argus
					0.5	0.79			
					1.5	2.4			
					5	7.9			
					Saline	–			
Comments: Bolus IV administration of tenecteplase at doses up to and including 5 mg/kg/day did not elicit maternal toxicity or developmental toxicity, including teratogenicity, when administered daily on Gestation Days (GDs) 6–10. Tenecteplase Vehicle did not elicit maternal toxicity or developmental toxicity, including teratogenicity, when administered daily on GDs 6–10, 11–14, or 15–18. Daily bolus intravenous administration of tenecteplase at doses ≥ 0.5 mg/kg/day produced maternal and fetal toxicity when administered on GDs 11–14 or 15–18 in rabbits.									
97-234-0218 (Argus 107-015)	Pregnant Rabbit Vehicle Study (non-GLP)	Rabbit Hra: (NZW) SPF	4-6/F	IV	0 (Vehicle w/ L-arginine)	NA	M3-RD622 (L-arginine)	1 month	Argus
					0 (Vehicle w/ D-arginine)	NA	27797-17 (D-arginine)		
Comments: Bolus IV administration of both tenecteplase Vehicles (L-arginine and D-arginine) was well tolerated and did not elicit maternal toxicity or gross developmental toxicity, when administered daily on GDs 6B18 in the rabbit. Use of Abbocath-T IV cannulas was well tolerated and did not elicit maternal mortalities or abortions.									

Table 9 Developmental Reproductive Studies (cont'd)

Study No.	Study Type	Species/ Strain	No./ Sex /Group	Route of Admin.	Dose (mg/kg)	Estimated Safety Factor[a] Body Weight Ratio	Lot No.	Study Duration	Study Location
97-177-0218 (Genentech)	Pregnant Rabbit Vehicle Study (non-GLP)	Rabbit Hra: (NZW) SPF	6/F	IV	0 (Vehicle w/ L-arginine)	NA	M3-RD622 (L-arginine)	22 days	Genentech
					0 (Vehicle w/ D-arginine)	NA	27797-29 (D-arginine)		
					Saline	NA			
Comments: Bolus IV administration of saline and both tenecteplase Vehicles (L-Arginine and D-Arginine) was well tolerated and did not elicit maternal toxicity when administered daily on GDs 6-18 in the rabbit. Animals were sacrificed on GD 22; normal litter sizes and number of resorptions were observed in all treatment groups.									
97-244-0218 (Genentech)	Pregnant Rabbit Toxicity Study (non-GLP)	Rabbit Hra: (NZW) SPF	4/F	IV	5	7.9	D9821AX	22 days	Genentech
Comments: Pregnant rabbits administered a single IV dose of 5 mg/kg tenecteplase on GDs 13, 14, 15, 16, or 17 did not demonstrate any signs of toxicity. Animals administered multiple intravenous doses of 5 mg/kg tenecteplase on GDs 13-15 demonstrated weight loss, perivaginal bleeding, and death by GD 16. Additionally, signs of pulmonary edema were evident in animals treated repeatedly with tenecteplase. However, multiple administrations of tenecteplase did not affect litter size. The adverse effects of tenecteplase in pregnant rabbits appear to be due to multiple doses of tenecteplase and not a single dose, administered on a specific day of gestation.									

[a] Estimated Safety Factor's were obtained by calculating the ratio of either dose, plasma exposure, or peak concentration in each species to the corresponding value for humans in the Phase II clinical trial.

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 mycocardial 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 I trial. Am Heart J 1999;137:786-91

PART III: CONSUMER INFORMATION

PrTNKase®
tenecteplase for injection

This leaflet is part III of a three-part "Product Monograph" published when TNKase was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TNKase. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TNKase (tenecteplase for injection) is used in adults to treat acute myocardial infarctions (heart attacks). Treatment should begin as soon as possible after symptoms start.

What it does:
TNKase belongs to a group of medicines called thrombolytics. This medicine is involved in the process to dissolve blood clots that have formed in the blood vessels of the heart. This helps to prevent the damage caused by heart attacks and when given at the right time it has been shown to save lives.

When it should not be used:
- if you are allergic to TNKase or any of the ingredients it contains

In addition, TNKase will not be given by your doctor if you have, or have recently had, an illness that increases your risk of bleeding, including:
- a bleeding disorder or recent history of bleeding
- stroke
- recent major surgery or trauma to your brain or spine
- brain tumour
- abnormality of the blood vessels or aneurysm
- severe high blood pressure

What the medicinal ingredient is:
tenecteplase

What the non-medicinal ingredients are:
L-arginine, phosphoric acid, polysorbate 20

What dosage forms it comes in:
A vial containing 50 mg (10,000 units) TNKase to be prepared for intravenous injection

WARNINGS AND PRECAUTIONS

BEFORE TNKase is given, your doctor will review the possible risks based on your medical condition and history, including if you have/had:
- recent major surgery
- stroke
- recent bleeding in the gastrointestinal or urinary systems
- recent trauma
- high blood pressure
- problems with your heart or heartbeat
- bleeding disorder
- severe liver failure
- pregnancy
- serious infection or inflammation
- advanced age
- taken medications that affect blood clotting

INTERACTIONS WITH THIS MEDICATION

Medications that affect blood clotting may increase the risk of bleeding prior to, during or after therapy with TNKase.

PROPER USE OF THIS MEDICATION

TNKase is given as a single injection into a vein. Your doctor will give TNKase as soon as possible after your chest pain starts.

Usual dose:
The doctor calculates your dose of TNKase according to your body weight, with a maximum dose of 50 mg (10,000 units). Acetylsalicylic acid (ASA) and heparin are usually given as part of your treatment.

Overdose:
In the event of overdose, there may be an increased risk of bleeding. Any patients receiving greater than the recommended dose should be carefully monitored.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TNKase can have side effects.

The most frequent side effect associated with TNKase is bleeding. Most of the time the bleeding is minor, however sometimes major bleeding can occur requiring blood transfusion or leading to instability in blood pressure which may decrease blood flow to organs. If major bleeding occurs, your doctor will stop any medications that can make bleeding worse. Death or permanent disability can occur in patients who experience stroke or other serious bleeding episodes.

Allergic-type reactions such as swelling of the skin and throat, rash or hives can occur.

Other serious side effects affecting the heart and lungs have been reported among patients receiving TNKase and are often caused by the underlying disease. These effects can be life-threatening and may lead to death.

This is not a complete list of side effects. For any unexpected effects while taking TNKase, contact your doctor or pharmacist.

HOW TO STORE IT

Store the vials below 30°C or in a refrigerator at 2°C - 8°C.

The reconstituted solution may be stored for 8 hours in a refrigerator at 2°C - 8°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at
www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789,
or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.rochecanada.com or by contacting the sponsor Hoffmann-La Roche Limited, at: 1-888-762-4388.

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