PRODUCT MONOGRAPH

PrTNKase®

Tenecteplase

Powder for Solution - 50 mg/Vial
Sterile, Lyophilized

Fibrinolytic Agent

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

Date of Approval:
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Manufactured by:
Genentech, Inc.
California, U.S.A.

Submission Control No: 120211

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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. Cell culture is carried out in nutrient medium containing the antibiotic gentamicin (65 mg/L). However, the presence of the antibiotic is not detectable in the final product (limit of detection is 0.67 µg/vial).

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) 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 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. 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

Nonclinical Pharmacology

In vitro, TNKase (tenecteplase) 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) 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]	Lot No.	Study Duration	Study Location
						Body Weight Ratio			
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.

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