RETAVASE- reteplase
Chiesi USA, Inc.

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

RETAVASE (reteplase) for injection, for intravenous use
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

RETAVASE is a tissue plasminogen activator (tPA) indicated for treatment of acute ST-elevation myocardial infarction (STEMI) to reduce the risk of death and heart failure. (1)
Limitation of Use: The risk of stroke may outweigh the benefit produced by thrombolytic therapy in patients whose STEMI puts them at low risk for death or heart failure. (1)

DOSAGE AND ADMINISTRATION

- Two 10 unit intravenous injections, each administered over 2 minutes, 30 minutes apart. (2.1)
- No other medication should be injected or infused simultaneously via the same intravenous line or added to the injection solution. (2.1)

DOSAGE FORMS AND STRENGTHS

For Injection: 10 units as a lyophilized powder in single-use vials for reconstitution co-packaged with Sterile Water for Injection, USP in 10 mL prefilled syringe. (3)

CONTRAINDICATIONS

- Do not use in patients with:
  - Active internal bleeding (4)
  - Recent stroke (4)
  - Recent intracranial or intraspinal surgery or serious head trauma (4)
  - Intracranial neoplasm, arteriovenous malformation, or aneurysm (4)
  - Known bleeding diathesis (4)
  - Severe uncontrolled hypertension (4)

WARNINGS AND PRECAUTIONS

- Increases the risk of bleeding. Avoid intramuscular injections. (5.1)
- Hypersensitivity (5.2)
- Cholesterol embolism (5.3)

ADVERSE REACTIONS

The most common adverse reaction (>5%) is bleeding. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pediatric Use: Safety and effectiveness have not been established. (8.4)

Revised: 4/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RETAVASE is indicated for use in acute ST-elevation myocardial infarction (STEMI) to reduce the risk of death and heart failure.

Limitation of Use: The risk of stroke may outweigh the benefit produced by thrombolytic therapy in patients whose STEMI puts them at low risk for death or heart failure.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information and Administration

As soon as possible after the onset of STEMI, administer 10 units intravenously over 2 minutes. Administer a second dose of 10 units 30 minutes after the first dose.

2.2 Reconstitution

Reconstitute RETAVASE immediately before administration.

Reconstitute RETAVASE only with the supplied Sterile Water for Injection. Slight foaming upon reconstitution may occur; if necessary allow the vial to stand undisturbed for

several minutes to allow dissipation of any large bubbles. Prior to administration, inspect the product for particulate matter and discoloration.

Use aseptic technique throughout.

Step 1: Open the package containing the reconstitution spike. Remove the protective cap from the luer lock port of the reconstitution spike and remove the protective cap on the end of the sterile 10 mL pre-filled syringe. Remove the protective flip-cap from one vial of RETAVASE.

Step 2: Clean the rubber closure with an alcohol wipe (not contained within kit).

Step 3: Connect the sterile pre-filled syringe to the reconstitution spike.

Step 4: Remove the protective cap from the spike end of the reconstitution spike and firmly insert the spike into the vial of RETAVASE.

Step 5: Connect the syringe plunger to the sterile 10 mL pre-filled syringe by screwing the plunger into the rubber stopper.

Step 6: Transfer the 10 mL of Sterile Water for Injection through the reconstitution spike into the vial of RETAVASE.

Step 7: With the reconstitution spike and empty pre-filled syringe still attached to the vial, swirl the vial gently until the contents are fully dissolved, may take up to 2 minutes. **DO NOT SHAKE**. Upon reconstitution, the solution should be clear and colorless. Discard if particulate matter or discoloration is observed. The resulting solution concentration is 1 unit/mL and delivers 10 mL (10 units reteplase).

Step 8: Disconnect the empty pre-filled syringe from the reconstitution spike and connect the plastic, graduated syringe to the reconstitution spike that is still attached to the vial.

Step 9: Withdraw 10 mL of RETAVASE reconstituted solution into the graduated syringe. A small amount of solution will remain in the vial due to overfill. Detach the graduated syringe from the reconstitution spike.

2.3 Heparin Incompatibility

Heparin and RETAVASE are incompatible. Do not administer RETAVASE through an intravenous line containing heparin.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 10 units as a lyophilized powder in single-use vials for reconstitution co-packaged with Sterile Water for Injection, USP in 10 mL prefilled syringe.

4 CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, RETAVASE is contraindicated in the following situations:

- Active internal bleeding
- Recent stroke
- Intracranial or intraspinal surgery or serious head trauma within 3 months

- Intracranial conditions that increase the risk of bleeding (e.g. neoplasms, arteriovenous malformation, or aneurysms)
- Bleeding diathesis
- Current severe uncontrolled hypertension

5 WARNINGS AND PRECAUTIONS

5.1 Bleeding

RETAVASE can cause significant and sometimes fatal bleeding. Avoid intramuscular injections and other trauma to a patient administered RETAVASE. Minimize venipunctures. Avoid puncturing noncompressible veins, such as the internal jugular and subclavian. If an arterial puncture is necessary, use an upper extremity vessel that is accessible to manual compression, apply pressure for at least 30 minutes, and monitor the puncture site closely. As fibrin is lysed during RETAVASE therapy, bleeding from recent puncture sites or other recent trauma may occur.

Should serious bleeding (not controllable by local pressure) occur, terminate concomitant anticoagulant therapy. Withhold the second RETAVASE dose if serious bleeding occurs before it is administered.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with RETAVASE administration. Signs and symptoms observed included rash, pruritis, erythema, glossal (tongue) edema, hypotension and respiratory distress. If an anaphylactoid reaction occurs, withhold the second dose of RETAVASE and initiate appropriate therapy.

5.3 Cholesterol Embolization

Cholesterol embolism has been reported in patients treated with thrombolytic agents. Cholesterol embolism may present with 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 and can be fatal. It is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy.

5.4 Drug/Laboratory Test Interactions

Coagulation tests and measures of fibrinolytic activity are unreliable during RETAVASE therapy unless specific precautions are taken to prevent *in vitro* artifacts. When present in blood at pharmacologic concentrations, RETAVASE remains active under *in vitro* conditions, which can result in degradation of fibrinogen in blood samples removed for analysis.

6 ADVERSE REACTIONS

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

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Cholesterol Embolization *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Bleeding

The most frequent adverse reaction associated with RETAVASE is bleeding.

- Intracranial hemorrhage *[see Clinical Studies (14)]*

In the INJECT clinical trial, the overall rate of in-hospital, intracranial hemorrhage was 0.8%. The risk for intracranial hemorrhage is increased in patients with advanced age (2.2% among patients >70 years old) or with elevated blood pressure (2.4% among patients with systolic blood pressure >160 mmHg).

- Other types of hemorrhage

The incidence of other types of bleeding events in clinical studies of RETAVASE varied depending upon the use of arterial catheterization or other invasive procedures and whether the study was performed in Europe or the USA. The overall incidence of any bleeding event in patients treated with RETAVASE in clinical studies (n = 3,805) was 21.1%. The rates for bleeding events, regardless of severity, for the 10 + 10 unit RETAVASE regimen from controlled clinical studies are summarized in Table 1.

Table 1: RETAVASE Hemorrhage Rates

Bleeding Site	INJECT	RAPID 1 and RAPID 2	
	Europe N = 2,965	USA N = 210	Europe N =113
Injection Site*	4.6%	48.6%	19.5%
Gastrointestinal	2.5%	9.0%	1.8%
Genitourinary	1.6%	9.5%	0.9%
Anemia, site unknown	2.6%	1.4%	0.9%

* includes the arterial catheterization site (all patients in the RAPID studies underwent arterial catheterization).

In these studies the severity and sites of bleeding events were similar for RETAVASE and the comparison thrombolytic agents.

Allergic Reactions

Among the 2,965 patients receiving RETAVASE in the INJECT trial, serious allergic reactions were noted in 3 patients, with one patient experiencing dyspnea and hypotension.

Among the 9,938 patients that received RETAVASE in a postmarketing clinical study, 8 patients experienced allergic and/or anaphylactoid reactions. Signs and symptoms observed included rash, pruritis, erythema, glossal (tongue) edema, hypotension, and respiratory distress.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data with RETAVASE use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, reteplase administered to pregnant rabbits resulted in hemorrhaging in the genital tract, leading to abortions in mid-gestation in doses 3 times the human dose; however, there was no evidence of fetal anomalies in rats at doses up to 15 times the human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Maternal Adverse Reactions

The most common complication of thrombolytic therapy is bleeding and pregnancy may increase this risk.

Data

Animal Data

Reteplase was administered to pregnant rabbits in doses 3 times the human dose (0.86 units/kg) resulting in hemorrhaging in the genital tract, leading to abortions in mid-gestation. In animal developmental studies in rats at Reteplase doses up to 15 times the human dose (4.31 units/kg), there was no evidence of fetal anomalies.

8.2 Lactation

Risk Summary

There are no data on the presence of reteplase in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. RETEVASE has not been studied in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness of RETAVASE in pediatric patients have not been established.

11 DESCRIPTION

Reteplase is a non-glycosylated deletion mutein of tissue plasminogen activator (tPA), containing the kringle 2 and the protease domains of human tPA. Reteplase contains 355 of the 527 amino acids of native tPA (amino acids 1-3 and 176-527). Reteplase is

produced by recombinant DNA technology in E. coli. The protein is isolated as inactive inclusion bodies from E. coli, converted into its active form by an *in vitro* folding process and purified by chromatographic separation. The molecular weight of Reteplase is 39,571 daltons.

Potency is expressed in units (U) using a reference standard which is specific for RETAVASE and is not comparable with units used for other thrombolytic agents.

RETAVASE (reteplase) for Injection is a sterile, white, lyophilized powder for intravenous injection after reconstitution with Sterile Water for Injection, USP (without preservatives). Following reconstitution with 10 mL of Sterile Water for Injection, the resulting concentration is 1 unit/mL to allow for delivery of 10 mL (10 units reteplase). The pH is 6.0 ± 0.3. RETAVASE is supplied with overfill to ensure sufficient drug for administration of each 10 unit injection.

Each single-use vial delivers:

Reteplase	10 units
Dipotassium Hydrogen Phosphate	131 mg
Phosphoric Acid	49.3 mg
Polysorbate 80	5 mg
Sucrose	350 mg
Tranexamic Acid	8 mg

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

RETAVASE is a recombinant plasminogen activator which catalyzes the cleavage of endogenous plasminogen to generate plasmin. Plasmin in turn degrades the fibrin matrix of the thrombus, thereby exerting its thrombolytic action.

12.2 Pharmacodynamics

In a controlled trial, 36 of 56 patients treated for myocardial infarction had a decrease in fibrinogen levels to below 100 mg/dL by 2 hours following the administration of RETAVASE as two intravenous injections (10 + 10 unit) in which 10 units was followed 30 minutes later by a second dose of 10 units. The mean fibrinogen level returned to the baseline value by 48 hours.

12.3 Pharmacokinetics

Based on the measurement of thrombolytic activity, RETAVASE is cleared from plasma at a rate of 250-450 mL/min, with an effective half-life of 13-16 minutes. RETAVASE is cleared primarily by the liver and kidney.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of RETAVASE. Studies to determine mutagenicity, chromosomal aberrations, gene mutations, and micronuclei induction were negative at all concentrations tested.

14 CLINICAL STUDIES

RETAVASE was evaluated in three controlled clinical studies comparing RETAVASE to other thrombolytic agents. In all three studies, patients were treated with aspirin (initial doses of 160 mg to 350 mg and subsequent doses of 75 mg to 350 mg) and heparin (a 5,000 unit IV bolus prior to the administration of RETAVASE or control, followed by a 1000 unit/hour continuous IV infusion for at least 24 hours).

The INJECT study compared RETAVASE to streptokinase on mortality rates at 35 days following acute ST-elevation myocardial infarction (STEMI). INJECT was a double-blind study in which 6,010 patients with no more than 12 hours of chest pain consistent with coronary ischemia and either ST segment elevation or bundle branch block on ECG were randomized 1:1 to RETAVASE (10 + 10 unit) or streptokinase (1.5 million units over 60 minutes). Patients with cerebrovascular or other bleeding risks or with systolic blood pressure >200 mm Hg or diastolic blood pressure >100 mm Hg were excluded from enrollment. The study was designed to determine whether the effect of RETAVASE on survival was noninferior to that of streptokinase by ruling out with 95% confidence that 35-day mortality among RETAVASE patients was no more than 1% higher than among streptokinase patients. The results of the primary endpoint (mortality at 35 days), 6-month mortality, and selected other in-hospital endpoints are shown in Table 2.

Table 2: INJECT Study: Selected Results

Endpoint	**RETAVASE N = 2,965**	**Streptokinase N = 2,971**	**RETAVASE-Streptokinase Δ (95% CI)**
35-day mortality*	8.9%	9.4%	-0.5 (-2.0, 0.9)
6-month mortality	11.0%	12.1%	-1.1 (-2.7, 0.6)
Cardiogenic shock	4.6%	5.8%	-1.2 (-2.4, -0.1)
Heart failure in-hospital	24.8%	28.1%	-3.3 (-5.6, -1.1)
Any stroke in-hospital	1.4%	1.1%	0.3 (-0.3, 0.8)
Intracranial hemorrhage in-hospital	0.8%	0.4%	0.4 (0.0, 0.8)

* Kaplan-Meier estimates

More patients treated with RETAVASE experienced hemorrhagic strokes than did patients treated with streptokinase. An exploratory analysis indicated that the incidence of intracranial hemorrhage was higher among older patients or those with elevated blood pressure.

The other two studies (RAPID 1 and RAPID 2) compared coronary artery patency of RETAVASE to two regimens of alteplase in patients with STEMI. In RAPID 1 patients within 6 hours of the onset of symptoms were randomized to open-label administration of one of three regimens of RETAVASE (doses of 10 + 10 unit, 15 unit, or 10 + 5 unit) or to alteplase (100 mg over 3 hours). In RAPID 2 patients within 12 hours of the onset

of symptoms were randomized to open-label administration of either RETAVASE (10 + 10 unit) or alteplase (100 mg over 1.5 hours). The primary endpoint for both studies was patency of the infarct-related artery 90 minutes after initiation of therapy. Interpretation of coronary angiograms was blinded.

A higher percentage of subjects administered RETEVASE had complete flow (TIMI grade 3) and partial or complete flow (TIMI grades 2 or 3) compared to both regimens of alteplase. The relationship between coronary artery patency and clinical efficacy has not been established.

In both clinical trials the re-occlusion rates were similar for RETAVASE and alteplase.

Table 3: RAPID 1 and RAPID 2 Studies: Angiographic Results

90 minute patency rates	**RAPID 2**			**RAPID 1***		
	RETAVASE (10 +10 unit) N = 157	**Alteplase** (100 mg over 1.5 hours) N = 146	**p-value**	**RETAVASE** (10 +10 unit) N = 142	**Alteplase** (100 mg over 3 hours) N = 145	**p-value**
TIMI 2 or 3	83%	73%	0.03	85%	77%	0.08
TIMI 3	60%	45%	0.01	63%	49%	0.02

* p values represent one of multiple dose comparisons.

16 HOW SUPPLIED/STORAGE AND HANDLING

RETAVASE (reteplase) for Injection is supplied as a sterile, preservative-free, lyophilized powder in 10 unit vials without a vacuum, in the following packaging configurations:

RETAVASE Kit (NDC 10122-141-02): 2 single-use RETAVASE vials 10 units, 2 single-use prefilled syringes for reconstitution (10 mL Sterile Water for Injection, USP), 2 syringe plungers, 2 sterile 10 mL graduated syringes, 2 sterile reconstitution spikes, 1 quick reference guide and 1 package insert.

RETAVASE Half-Kit (NDC 10122-143-01): 1 single-use RETAVASE vial 10 units, 1 single-use prefilled syringe for reconstitution (10 mL Sterile Water for Injection, USP), 1 syringe plunger, 1 sterile 10 mL graduated syringe, 1 sterile reconstitution spike, 1 quick reference guide and 1 package insert.

Storage: Store RETAVASE at 2°C to 25°C (36°F to 77°F). The box should remain sealed until use to protect the lyophilisate from exposure to light.

Manufactured by:

Chiesi USA, Inc.

Cary, NC 27518

U.S. License No. 2150

Retavase® manufactured at Patheon Italia, S.p.A., Monza, Italy 20900.

To report an adverse event, record the lot number and call Medical Information at 1-888-

661-9260.

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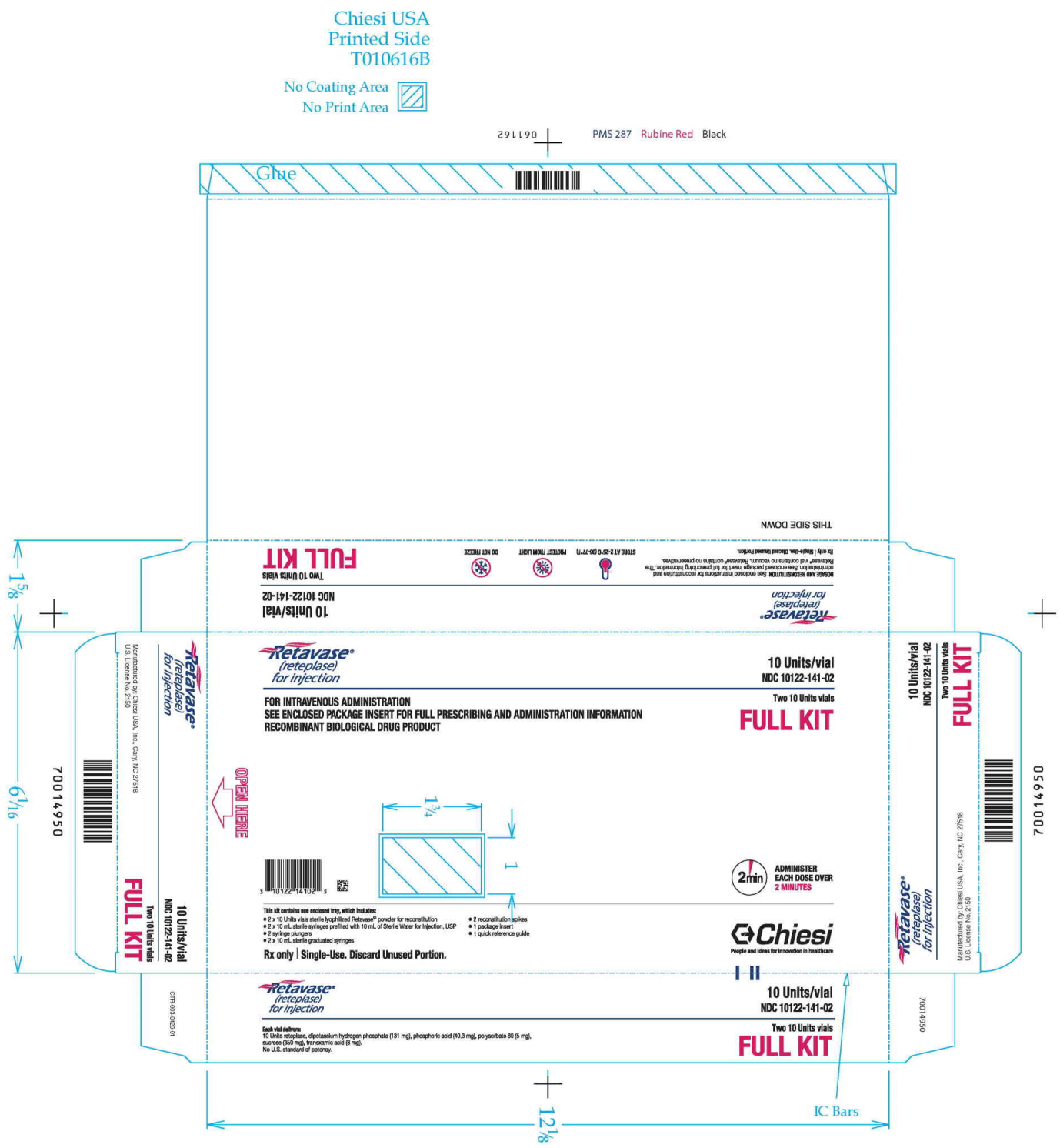
CTR-001-0422-03-SPL

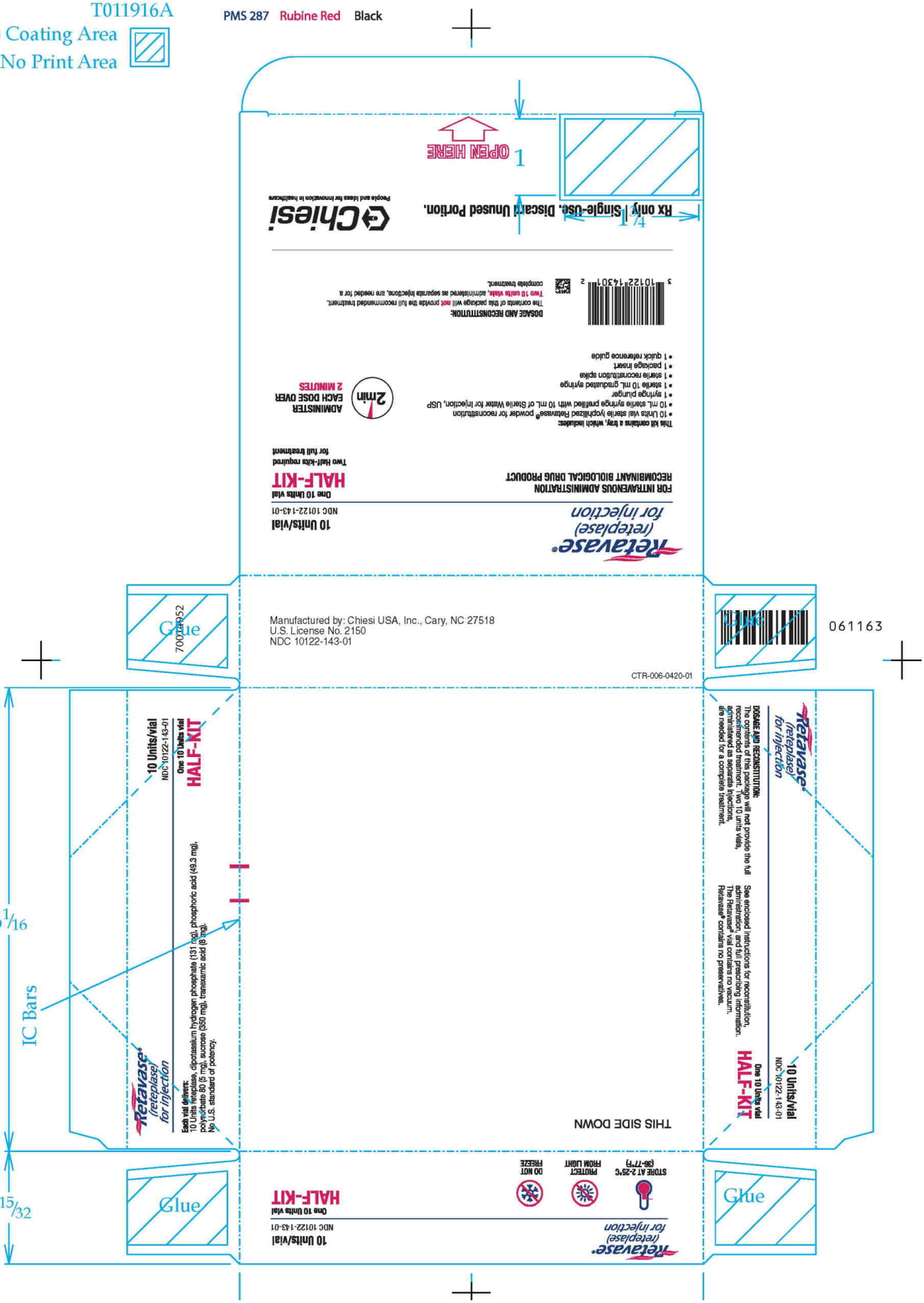
Retavase Full Kit



Retavase Half Kit

Chiesi USA
Printed Side
T011916A
No Coating Area
No Print Area

PMS 287 Rubine Red Black



RETAVASE
reteplase kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10122-143

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:10122-143-01	1 in 1 BOX; Type 1: Convenience Kit of Co-Package	10/30/1996	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-USE	10 mL
Part 2	1 SYRINGE	10 mL

Part 1 of 2

RETAVASE
reteplase injection, powder, lyophilized, for solution

Product Information

Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RETEPLASE (UNII: DQA630RIE9) (RETEPLASE - UNII:DQA630RIE9)	RETEPLASE	1.81 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
DIBASIC POTASSIUM PHOSPHATE (UNII: CI71S98N1Z)	131 mg in 1 mL
PHOSPHORIC ACID (UNII: E4GA8884NN)	49.3 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	5 mg in 1 mL
SUCROSE (UNII: C151H8M554)	350 mg in 1 mL
TRANEXAMIC ACID (UNII: 6T84R30KC1)	8 mg in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		10 mL in 1 VIAL, SINGLE-USE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103786		

Part 2 of 2

STERILE WATER

water injection, solution

Product Information	
Item Code (Source)	NDC:10122-142
Route of Administration	INTRAVENOUS

Inactive Ingredients	
Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	1 mL in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:10122-142-01	10 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103786		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

BLA	BLA103786	10/30/1996	

RETAVASE

reteplase kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:10122-141

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:10122-141-02	1 in 1 BOX; Type 1: Convenience Kit of Co-Package	10/30/1996	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	2 VIAL, SINGLE-USE	20 mL
Part 2	2 SYRINGE	20 mL

Part 1 of 2

RETAVASE

reteplase injection, powder, lyophilized, for solution

Product Information	
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
RETEPLASE (UNII: DQA630RIE9) (RETEPLASE - UNII:DQA630RIE9)	RETEPLASE	1.81 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DIBASIC POTASSIUM PHOSPHATE (UNII: CI71S98N1Z)	131 mg in 1 mL
PHOSPHORIC ACID (UNII: E4GA8884NN)	49.3 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	5 mg in 1 mL
SUCROSE (UNII: C151H8M554)	350 mg in 1 mL
TRANEXAMIC ACID (UNII: 6T84R30KC1)	8 mg in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		10 mL in 1 VIAL, SINGLE-USE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103786		

Part 2 of 2

STERILE WATER

water injection, solution

Product Information	
Item Code (Source)	NDC:10122-142
Route of Administration	INTRAVENOUS

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:10122-142-01	10 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103786		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103786	10/30/1996	

Labeler - Chiesi USA, Inc. (088084228)

Registrant - Chiesi USA, Inc. (088084228)

Revised: 4/2022

Chiesi USA, Inc.