

Reteplase-Recombinant Tissue Plasminogen Activator - 18 mg

MIREL™

Prescribing Information

DESCRIPTION

MIREL™ (Reteplase) is a non-glycosylated deletion mutein of tissue plasminogen activator, containing the kringle 2 and the protease domains of human tissue plasminogen activator. Reteplase contains 355 of the 527 amino acids of native tissue plasminogen activator (amino acids 1-3 and 176-527). Reteplase is produced by recombinant DNA technology in *E. coli*. The protein is isolated as 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.

COMPOSITION

MIREL™ is a sterile, white, lyophilized powder for intravenous bolus injection after reconstitution with sterile water for injection.

Each vial contains

Reteplase (Recombinant Tissue Plasminogen Activator).... 18 mg along with Tranexamic Acid, Dipotassium Hydrogen Phosphate, Phosphoric Acid, Sucrose and Polysorbate 80 as excipients.

PHARMACOLOGY

Mechanism of Action

Reteplase is a recombinant plasminogen activator. It catalyzes the cleavage of endogenous plasminogen to generate plasmin. This plasminogenolysis takes place in the presence of fibrin. Plasmin in turn degrades fibrin, which is the main component of the matrix of thrombi, thereby exerting its thrombolytic action.

Clinical study on **MIREL™** (Reteplase) demonstrated efficacy by reducing mortality in patients with ST segment elevation myocardial infarction (STEMI). **MIREL™** (Reteplase) also decreased the frequency of re-infarction, cardiac failure, cardiac arrhythmia and need for recanalization procedure which is comparable with earlier reported Reteplase studies. There was also significant increase in LVEF and 50% lowering of ST segment in >50% of patients at 90th minute post dosing.

Pharmacokinetics:

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

INDICATIONS

Reteplase is indicated for the thrombolytic treatment in patients with persistent ST segment elevation acute myocardial infarction and / or recent left Bundle Branch Block. Treatment should be initiated as soon as possible after the onset of acute myocardial infarction (AMI).

CONTRAINDICATIONS

Reteplase should not be used in patients having hypersensitivity to reteplase, polysorbate 80 or any of the other ingredients. Because thrombolytic therapy increases the risk of bleeding, **MIREL™** is contraindicated in the following situations:

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

ADVERSE EFFECTS

The most commonly reported adverse drug reaction associated with reteplase treatment is hemorrhage, predominantly at the injection site. Intracranial bleeding has been seen with reteplase therapy, which may be fatal in some cases. Systolic blood pressure over 160 mm Hg before thrombolysis with reteplase was associated with greater risk for cerebral bleeding. As age increases the risk of intracranial bleeding and fatal intracranial bleeding increases.

Patients administered Reteplase as treatment for myocardial infarction have experienced many events which are frequent sequelae of myocardial infarction and may or may not be attributable to Reteplase therapy. These events include cardiogenic shock, arrhythmias (e.g., sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation), AV block, pulmonary edema, heart failure, cardiac arrest, recurrent ischemia, reinfarction, myocardial rupture, mitral regurgitation, pericardial effusion, pericarditis, cardiac tamponade, venous thrombosis and embolism, and electromechanical dissociation. Allergic reactions were noted in clinical studies in a small number of patients.

Clinical study with **MIREL™** (Reteplase) demonstrated it to be safe, well tolerated and easy to administer. The safety profile was comparable with earlier reported Reteplase studies. Bleeding events with **MIREL™** (Reteplase) therapy were in 7.50%, which is comparable to earlier reported studies and only 2.50% patients, required blood transfusion. No stroke event was reported in this study. Other cardiac complications reported in the study were hypertension (12.50%), hypertension (10.00%), pericarditis (2.50%), bradycardia (8.75%) and thrombosis (2.50%).

WARNINGS AND PRECAUTIONS

Bleeding is the most common complication encountered during Reteplase therapy. The sites of bleeding include both internal bleeding sites (intracranial, retroperitoneal, gastrointestinal, genitourinary, or respiratory) and superficial bleeding sites (venous cut downs, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin and other anticoagulation may contribute to bleeding.

Thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites).

Should an arterial puncture be necessary during the administration of Reteplase, 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.

Other venipunctures should be performed carefully and only as required.

In case of serious bleeding which is not controllable by local pressure, concomitant anticoagulant therapy should be terminated immediately. In addition, the second bolus of Reteplase should not be given if serious bleeding occurs before it is administered.

Each patient considered for therapy with Reteplase should be carefully evaluated and anticipated benefits weighed against the potential risks associated with therapy. In the following conditions, the potential risks of

Reteplase therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy
- Previous puncture of noncompressible vessels
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Hypertension: systolic BP 180 mm Hg and/or diastolic BP 110 mm Hg
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Severe hepatic or renal dysfunction
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at a seriously infected site
- Age over 75 years
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Coronary thrombolysis may result in arrhythmias associated with reperfusion. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when Reteplase is administered. Cholesterol embolism has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown.

Pregnancy and lactation

Pregnancy Category C: Reteplase has been shown to have an abortifacient effect in rabbits when given in doses 3 times the human dose. Reproduction studies performed in rats at doses up to 15 times the human dose revealed no evidence of fetal anomalies; however, Reteplase administered to pregnant rabbits resulted in hemorrhage in the genital tract, leading to abortions in mid-gestation. There are no adequate and well controlled studies in pregnant women. Reteplase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether Reteplase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Reteplase is administered to a nursing woman.

DRUG INTERACTIONS

Interaction study reports with reteplase and medicinal product commonly administered in patients with acute myocardial infarction are not available. Heparin, vitamin K antagonists and medicinal product that alter platelet function (such as acetylsalicylic acid, dipyridamole and abciximab) may increase the risk of bleeding if administered prior to, during or after reteplase therapy.

OVERDOSAGE

In the event of over dosage one might expect depletion of fibrinogen and other blood coagulation components (e.g. coagulation factor V) with a consequent risk of bleeding.

INCOMPATIBILITIES

Heparin and Reteplase are incompatible when combined in solution. Do not administer heparin and Reteplase simultaneously in the same intravenous line.

If Reteplase is to be injected through an intravenous line containing heparin, a normal saline or 5% dextrose (D5W) solution should be flushed through the line prior to and following the Reteplase injection.

DOSAGE AND ADMINISTRATION

Reteplase is for intravenous administration only. Reteplase is administered as two bolus injections of 10 units each. Each bolus is administered over 2 minutes. The second bolus is given 30 minutes after the first bolus injection. No other medication should be injected or infused in the same intravenous line. No other medication should be added to the injection solution containing Reteplase. There is no experience with patients receiving repeat courses of therapy with Reteplase.

If Reteplase is to be injected through an intravenous line containing heparin, a normal saline or 5% dextrose (D5W) solution should be flushed through the line prior to and following the Reteplase injection. Although the value of anticoagulants and antiplatelet drugs during and following administration of Reteplase has not been studied, heparin has been administered concomitantly in most of the patients. Aspirin has been given either during and/or following heparin treatment.

HOW SUPPLIED

Each **MIREL™** kit contains, 2 single-use reteplase vials of 18 mg (10 units), 2 single-use diluent vials for reconstitution (10 ml sterile water for injection, IP), 2 sterile 10 mL syringes, 4 sterile needles and a package insert.

Reconstitution - Reteplase Kit:

Each vial should be reconstituted with 10 mL of sterile water for injection (WFI) in the following manner

- Step 1:** Remove the protective flip-cap from one vial of **MIREL™**
- Step 2:** Withdraw 10 mL of sterile water for injection from the supplied container into a sterile 10 mL syringe with sterile needle provided in the kit.
- Step 3:** Clean the rubber cap of **MIREL™** vial and pierce the rubber cap with the syringe needle containing WFI and allow the WFI to transfer into the vial. Ensure all the WFI is transferred into the vial.
- Step 4:** Remove the needle and syringe from the vial. Gently swirl the contents of the vial for dissolution. Do not shake or vortex. Repeat gentle swirling till all the contents are dissolved.
- Step 5:** Allow the vial to stand for few seconds for dissipation of air bubbles.
- Step 6:** Attach a fresh sterile needle to the syringe and withdraw the reconstituted solution into the syringe.
- Step 7:** The 10 mL bolus is now ready for administration.
- Step 8:** After 30 minutes the same steps to be followed for the second bolus injection.

When reconstituted as directed, **MIREL™** should be used within 4 hours. Prior to administration, the product should be visually inspected for particulate matter and discoloration.

STORAGE

Store **MIREL™** at 2-8°C (36-46°F). Prevent exposure to light. Do not use beyond the expiration date.

Shelf Life

2 years from the date of manufacturing.



Reliance Life Sciences Pvt. Ltd.