For the use of a Registered Medical Practitioner only

℞ Abciximab

AbcixiRel®

(Solution for injection in vial)

GENERIC NAME

Abciximab

DESCRIPTION

AbcixiRel® (Abciximab) is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP)IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin (αVβ3) receptor found on platelets and vessel wall endothelial and smooth muscle cells.

AbcixiRel® is a clear, colourless, sterile, non-pyrogenic solution for intravenous (IV) use.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each singe use vial contains:

Composition	Quantity per vial
Abciximab	10 mg
Sodium Phosphate buffer*	10 mM
Sodium Chloride	43.8 mg
Polysorbate 80	10 ppm
Water for Injection q.s.	5.0 ml

*Sodium phosphate buffer prepared from sodium hydroxide and phosphoric acid, pH 7.2

DOSAGE FORM AND STRENGTH

Solution for injection in vial (10 mg).

PHARMACOLOGICAL PROPERTIES

Mechanism of action and pharmacodynamic properties

Abciximab inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets. The mechanism of action is thought to involve steric hindrance and/or conformational effects to block access of large molecules to the receptor rather than direct interaction with the RGD (arginine-glycine-aspartic acid) binding site of GPIIb/IIIa.

Abciximab binds with similar affinity to the vitronectin receptor, also known as the αvβ3 integrin. The vitronectin receptor mediates the procoagulant properties of platelets and the proliferative properties of vascular endothelial and smooth muscle cells. Abciximab also binds to the activated Mac-1 receptor on monocytes and neutrophils. In addition, the degree of activated Mac-1 expression on circulating leukocytes and the numbers of circulating leukocyte-platelet complexes has been shown to be reduced in patients treated with Abciximab.

platelet receptors and fully inhibited platelet aggregation. The inhibitory effects of Abciximab were considered to be reversible by the transfusion of platelets. The antithrombotic efficacy of prototype antibodies [murine 7E3 Fab and F(ab')2] and AbcixiRel® was evaluated in dog, monkey and baboon models of coronary, carotid, and femoral artery thrombosis.

The non-clinical toxicology program included single dose toxicity studies in rats and mice, repeated dose studies in rats and rabbits and a skin sensitization study in guinea pigs. In addition, antibody estimation was performed as a part of immunogenicity responses in repeated dose toxicity studies.

No adverse acute toxicity was observed in Wistar rats and in Swiss albino mice at a dose level of 30 mg/kg. The repeated dose studies were conducted in Wistar rats and New Zealand white rabbits. There were no treatment related adverse changes observed in the study upto a dose level of 10 mg/kg and considered No Observed Adverse Effect Level (NOAEL). Similarly repeated dose toxicity study conducted in a second species i.e., rabbit, did not indicate any treatment related adverse changes at the highest dose (3 mg/kg) tested.

The serum antibody determination revealed almost comparable abciximab reactive antibody concentrations among all dosage groups in the rats. In case of rabbits, a dose proportional increase was observed in the antibody generation. Skin sensitization study conducted using undiluted concentration (5.86 mg/ml) of AbcixiRel® in guinea pigs did not reveal any kind of sensitization reactions.

CONTRAINDICATIONS

Because Abciximab may increase the risk of bleeding, it is contraindicated in the following clinical situations:

- Active internal bleeding.
- Recent (within six weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance.
- History of cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit.
- Bleeding diathesis.
- Administration of oral anticoagulants within seven days, unless prothrombin time is ≤ 1.2 times the control.
- Thrombocytopenia (< 100,000 cells/μl).
- Recent (within six weeks) major surgery or trauma.
- Intracranial neoplasm, arteriovenous malformation, or aneurysm.
- Severe uncontrolled hypertension.
- Presumed or documented history of vasculitis.
- Use of intravenous dextran before PCI, or intent to use it during an intervention.

Abciximab is also contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

Pharmacokinetics
As per published data, following intravenous bolus administration, free plasma concentrations of Abciximab decrease rapidly with an initial half-life of less than 10 minutes and a second phase half-life of about 30 minutes, probably related to rapid binding to the platelet GPIIb/IIIa receptors.

Platelet function generally recovers over the course of 48 hours, although Abciximab remains in the circulation for 15 days or more in a platelet-bound state. Intravenous administration of a 0.25 mg/kg bolus dose of Abciximab followed by continuous infusion of 10 μg/min (or a weight-adjusted infusion of 0.125 μg/kg/min to a maximum of 10 μg/min) produces approximately constant free plasma concentrations throughout the infusion. At the termination of the infusion period, free plasma concentrations fall rapidly for approximately six hours then decline at a slower rate.

CLINICAL PARTICULARS

Therapeutic indications
Abciximab is indicated as an adjunct to percutaneous coronary intervention (PCI) for the prevention of cardiac ischaemic complications:-

- in patients undergoing percutaneous coronary intervention.
- in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours.

Safety and efficacy of Abciximab use in patients not undergoing percutaneous coronary intervention have not been established.

Posology and method of administration
The safety and efficacy of Abciximab have only been investigated with concomitant administration of heparin and aspirin. In patients with failed PCIs, the continuous infusion of Abciximab should be stopped because there is no evidence for Abciximab efficacy in this setting.
In the event of serious bleeding that cannot be controlled by compression, Abciximab and heparin should be discontinued immediately.

The recommended dosage of Abciximab in adults is a 0.25 mg/kg intravenous bolus administered 10-60 minutes before the start of PCI, followed by a continuous intravenous infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 hours.
Patients with unstable angina not responding to conventional medical therapy and who are planned to undergo PCI within 24 hours may be treated with an Abciximab 0.25 mg/kg intravenous bolus followed by an 18- to 24-hour intravenous infusion of 10 μg/min, concluding one hour after the PCI.

Parenteral drug product should be inspected visually for particulate matter prior to administration. Preparations containing visibly opaque particles should not be used.
Withdraw the necessary amount of AbcixiRel® for bolus injection into a syringe. Filter the bolus injection using a sterile, non-pyrogenic, low protein-binding, 0.2 or 0.45 micron syringe filter.
Withdraw the necessary amount of AbcixiRel® for the continuous infusion into a syringe. Inject into an appropriate container of sterile 0.9% saline or 5% dextrose and infuse at the calculated rate via a continuous infusion pump. The continuous infusion should be filtered either upon admixture using a sterile, non-pyrogenic, low protein-binding, 0.2 or 0.45 micron syringe filter or during administration using an in-line, sterile, non-pyrogenic, low protein-binding, 0.2 or 0.45 micron filter. Discard the unused portion at the end of the infusion.

NONCLINICAL PROPERTIES

Animal toxicology or pharmacology
In non-human primates, AbcixiRel® bolus doses of 0.25 mg/kg generally achieved a blockade of at least 80% of

CLINICAL STUDY
A prospective, multi-centric, open-label, two arm, parallel group, active control, randomized comparative clinical study was conducted for AbcixiRel® to evaluate the comparative efficacy and safety of AbcixiRel® and the Innovator product in 104 patients undergoing percutaneous coronary intervention. Either drug was administered before 10-60 min of PCI procedure as intravenous bolus and was continued until 12 hrs as slow intravenous infusion. All patients were assessed for composite or cumulative incidence of death from any cause, myocardial infarction and re-infarction or severe myocardial ischemia requiring urgent coronary bypass surgery or repeated percutaneous coronary re-vascularization within 30 days (primary objective).
In the primary analysis, for both AbcixiRel® as well as comparator arms, there was no event reported for death, myocardial infarction and re-infarction or severe myocardial ischemia requiring urgent coronary by-pass surgery or repeated PCI.
In both the treatment arms, there was no event reported for secondary outcomes of nonfatal myocardial infarction and repeated PCI.
In both the arms, there was significant rise in bleeding time from baseline to 12 hrs and after that, it declined. At 40 hrs, bleeding time value was near to normal in both the treatment arms.
The most commonly reported adverse events (≥ 5%) were hematoma, pyrexia in AbxiciRel® arm and angiopathy, pyrexia, asthenia, pain in extremity in comparator arm. There was no atypical adverse event reported in the study in any of the treatment arms. There was no infusion related adverse event reported in the study.

UNDESIRABLE EFFECTS

Bleeding
Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., heparin, other anticoagulants or thrombolytics. Bleeding in the previous studies was classified as major, minor or insignificant by the criteria of the Thrombolysis in Myocardial Infarction study group.

Major bleeding events were defined as either an intracranial haemorrhage or a decrease in haemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross haematuria, spontaneous haematemesis, observed blood loss with a haemoglobin decrease of more than 3 g/dL, or a decrease in haemoglobin of at least 4 g/dL without an identified bleeding site. Insignificant bleeding events were defined as a decrease in haemoglobin of less than 3 g/dL or a decrease in haemoglobin between 3-4 g/dL without observed bleeding.

Major bleeding occurred in 10.6% of patients given Abciximab bolus plus infusion. Minor bleeding was seen in 16.8% of Abciximab bolus plus infusion patients.

Although data are limited, Abciximab treatment was not associated with excess major bleeding in patients who underwent CABG surgery.

Pulmonary alveolar haemorrhage has been rarely reported during use of Abciximab. This can present with any or all of the following in close association with Abciximab administration: hypoxemia, alveolar infiltrates on chest x-ray, haemoptysis, or an unexplained drop in haemoglobin.

Intracranial Haemorrhage and Stroke
Intracranial haemorrhage is observed with abciximab which is a major bleeding event.

Thrombocytopenia
Among patients in previous studies who were treated with Abciximab plus low-dose heparin, the proportion of patients with any thrombocytopenia (platelets less than

100,000 cells/μL) ranged from 2.5 to 3.0%. The incidence of severe thrombocytopenia (platelets less than 50,000 cells/μL) ranged from 0.4 to 1.0% and platelet transfusions were required in 0.9 to 1.1%, respectively.

OTHER ADVERSE REACTIONS
The following additional adverse events were reported in published studies for patients treated with a bolus plus infusion of Abciximab at incidences which were less than 0.5% higher than for patients in the placebo arm.

Cardiovascular system: Ventricular tachycardia (1.4%), pseudoaneurysm (0.8%), palpitation (0.5%), arteriovenous fistula (0.4%), incomplete AV block (0.3%), nodal arrhythmia (0.2%), complete AV block (0.1%), embolism (limb) (0.1%); thrombophlebitis (0.1%).

Gastrointestinal system: Dyspepsia (2.1%), diarrhoea (1.1%), ileus (0.1%), gastroesophogeal reflux (0.1%); Haemic and Lymphatic System: anaemia (1.3%), leukocytosis (0.5%), petechiae (0.2%).

Nervous system: Dizziness (2.9%), anxiety (1.7%), abnormal thinking (1.3%), agitation (0.7%), hypesthesia (0.6%), confusion (0.5%) muscle contractions (0.4%), coma (0.2%), hypertonia (0.2%), diplopia (0.1%).

Respiratory system: Pneumonia (0.4%), rales (0.4%), pleural effusion (0.3%), bronchitis (0.3%), bronchospasm (0.3%), pleurisy (0.2%), pulmonary embolism (0.2%), rhonchi (0.1%).

Musculoskeletal system: Myalgia (0.2%).

Urogenital system: Urinary retention (0.7%), dysuria (0.4%), abnormal renal function (0.4%), frequent micturition (0.1%), cystalgia (0.1%), urinary incontinence (0.1%), prostatitis (0.1%).

Miscellaneous: Pain (5.4%), sweating increased (1.0%), asthenia (0.7%), incisional pain (0.6%), pruritus (0.5%), abnormal vision (0.3%), oedema (0.3%), wound (0.2%), abscess (0.2%), cellulitis (0.2%), peripheral coldness (0.2%), injection site pain (0.1%), dry mouth (0.1%), pallor (0.1%), diabetes mellitus (0.1%), hyperkalemia (0.1%), enlarged abdomen (0.1%), bullous eruption (0.1%), inflammation (0.1%), drug toxicity (0.1%).

IMMUNOGENICITY
As with all therapeutic proteins, there is a potential for immunogenicity in patients receiving a first exposure to Abciximab. No increase in hypersensitivity or allergic reactions was observed with Abciximab treatment.
Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Abciximab with the incidence of antibodies to other products may be misleading.

Based on an integrated analysis of data from all studies, the following guidelines may be utilized to minimize the risk for bleeding:

When Abciximab is initiated 18 to 24 hours before PCI, the APTT should be maintained between 60 and 85 seconds during the Abciximab and heparin infusion period.

During PCI, the ACT should be maintained between 200 and 300 seconds.

If anti-coagulation is continued in these patients following PCI, the APTT should be maintained between 55 and 75 seconds.

Re-administration
Administration of Abciximab may result in the formation of Human Antichimeric Antibody (HACA) that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia or diminished benefit upon re-administration of Abciximab.

Carcinogenesis, mutagenesis and impairment of fertility
In vitro and in vivo mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in animals have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals.

USE IN SPECIAL POPULATION:
Pregnancy category C
Animal reproduction studies have not been conducted with Abciximab. It is also not known whether Abciximab can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Abciximab should be given to a pregnant woman only if clearly needed.

Nursing mothers
It is not known whether this drug is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Abciximab is administered to a nursing mother.

Paediatric use
Safety and effectiveness in paediatric patients have not been studied.

Geriatric use
The clinical experience is not adequate to determine whether patients of age 75 or greater respond differently than younger patients.

Effects on ability to drive and use machines
Not relevant

OVERDOSE
There has been no experience of overdosage in human studies

DRUG INTERACTIONS

Formal drug interaction studies with Abciximab have not been conducted. Abciximab has been administered to patients with ischaemic heart disease treated concomitantly with a broad range of medications used in the treatment of angina, myocardial infarction and hypertension. These medications include heparin, warfarin, beta-adrenergic receptor blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, intravenous and oral nitrates, ticlopidine, and aspirin. Heparin, other anticoagulants, thrombolytics and antiplatelet agents are associated with an increase in bleeding.

SPECIAL WARNINGS AND PRECAUTIONS

Bleeding events

Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants, or thrombolytics. The risk of major bleeds due to Abciximab therapy is increased in patients receiving thrombolytics and should be weighed against the anticipated benefits.

Should serious bleeding occur that is not controllable with pressure, the infusion of Abciximab and any concomitant heparin should be stopped.

To minimize the risk of bleeding with Abciximab, it is important to use a low-dose, weight-adjusted heparin regimen, a weight-adjusted Abciximab bolus and infusion, strict anticoagulation guidelines, careful vascular access site management, discontinuation of heparin after the procedure and early femoral arterial sheath removal. Therapy with Abciximab requires careful attention to all potential bleeding sites including catheter insertion sites, arterial and venous puncture sites, cutdown sites, needle puncture sites, and gastrointestinal, genitourinary, pulmonary (alveolar), and retroperitoneal sites.
Because Abciximab inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, dipyridamole, and ticlopidine.

Allergic reactions (including anaphylaxis)

Allergic reactions, some of which were anaphylaxis (sometimes fatal), have been reported rarely in patients treated with Abciximab. Patients with allergic reactions should receive appropriate treatment. Treatment of anaphylaxis should include immediate discontinuation of Abciximab administration and initiation of resuscitative measures.

Thrombocytopenia

Thrombocytopenia, including severe thrombocytopenia, has been observed with Abciximab administration. Platelet counts should be monitored prior to, during, and after treatment with Abciximab. Acute decreases in platelet count should be differentiated between true thrombocytopenia and pseudothrombocytopenia. If true thrombocytopenia is verified, Abciximab should be immediately discontinued and the condition appropriately monitored and treated.

In the event of serious uncontrolled bleeding or the need for emergency surgery, Abciximab should be discontinued. If platelet function does not return to normal, it may be restored, at least in part, with platelet transfusions.

Laboratory tests

Before infusion of Abciximab, prothrombin time, Activated Clotting Time (ACT), Activated Partial Thromboplastin Time (APTT), and platelet count should be measured to identify pre-existing haemostatic abnormalities.

PHARMACEUTICAL PROPERTIES

Incompatibilities

Abciximab should be administered in a separate intravenous line whenever possible and not mixed with other medications.

Packing information

AbcixiRel® (abciximab) 2 mg/ml is supplied in 5 ml vial containing 10 mg abciximab.

Storage and handling information

Vials should be stored at 2°C to 8°C (36°F to 46.8°F). Do not freeze. Do not shake. Do not use beyond the expiration date. Discard any unused portion left in the vial. Discard into appropriate containers.

Shelf-life

For details of product's shelf life, please refer to Expiry Date mentioned on the label and carton.

PATIENT COUNSELLING INFORMATION

- Discuss specific use of drug and side effects with patient as it relates to treatment.
  - o Bleeding risk: Abciximab has the potential to increase the risk of bleeding events, rarely including those with a fatal outcome, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants. The risk of major bleeds due to Abciximab therapy is increased in patients receiving thrombolytics and should be weighed against the anticipated benefits. Thrombocytopenia, including severe thrombocytopenia, has been observed with Abciximab administration
  - o Allergic reactions: Anaphylaxis (sometimes fatal), have been reported rarely in patients treated with abciximab.
- Patient may experience back pain, nausea, vomiting, or headache. Have patients report immediately to prescriber, signs of bleeding (vomiting blood or vomit that looks like coffee grounds; coughing up blood; hematuria; black, red, or tarry stools; bleeding from the gums; abnormal vaginal bleeding; bruises without a reason or that get bigger; or any severe or persistent bleeding), severe dizziness, passing out, angina, bradycardia, fall or crash-hitting head, or severe loss of strength and energy.

DETAILS OF MANUFACTURER

Reliance Life Sciences Pvt. Ltd.
DALC, Plant 2, R-282, TTC Area of MIDC, Thane-Belapur Road, Rabale, Navi Mumbai - 400 701, INDIA.

DETAILS OF PERMISSION AND/OR LICENCE NUMBER WITH DATE

Form 46 Permission MF-87/2013 dated 23 Apr 2013
License # KD/7

DATE OF REVISION

September 2020

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