

Revasc[®]

15 mg desirudin powder and solvent for solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Revasc contains 15 mg desirudin (INN) corresponding to approximately 270 000 antithrombin units (ATU) or 18 000 ATU per mg of desirudin with reference to the WHO Second International Standard for α -thrombin. Desirudin is a recombinant DNA product derived from yeast cells.

Desirudin is a single chain polypeptide consisting of 65 amino acid residues and 3 disulphide bridges.

PHARMACEUTICAL FORM

Powder for injection to be reconstituted prior to subcutaneous injection with 0.5 mL mannitol solvent (3%) which is supplied with the product.

INDICATION

Prevention of thromboembolic complications after orthopaedic surgery.

POSODOGY AND METHOD OF ADMINISTRATION

Adult and Elderly Patients:

The recommended dose is 15 mg twice daily. The first injection should be initiated 5 to 15 minutes before surgery but after induction of regional block anaesthesia, if used. Treatment with desirudin is then continued twice daily post-operatively for 9 to a maximum of 12 days or until the patient is fully ambulant, whichever occurs first. Currently, there is no clinical experience to support the use of desirudin beyond 12 days.

Administration is by subcutaneous injection, preferable at an abdominal site. Injections should be rotated between at least four different sites.

Children:

There is no clinical experience with desirudin in children.

Patients with Renal Impairment:

Desirudin is contraindicated in patients with severe renal impairment (creatinine clearance of less than 30 ml/min corresponding to a serum creatinine \square 2.5 mg/dl or 221 micromol/l). In patients with mild or moderate renal impairment (creatinine clearance between 31 and 90 ml/min; see Precautions) activated partial thromboplastin time (aPTT) should be monitored.

Patients with Liver Impairment:

Desirudin is contraindicated in severe hepatic impairment. In patients with mild to moderate liver impairment (see Precautions) aPTT monitoring is recommended.

CONTRAINDICATIONS

Desirudin is contraindicated in patients with known hypersensitivity to natural or recombinant hirudins or to any of the excipients, in patients with active bleeding and/or irreversible coagulation disorders, in severe renal and hepatic impairment and during pregnancy (see Pregnancy and lactation). Desirudin is also contraindicated in patients with severe uncontrolled hypertension and subacute bacterial endocarditis.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Warnings:

Desirudin should not be administered by intramuscular injection owing to the risk of local haematoma, and intramuscular injections with any agent should be avoided during REVASC therapy.

Desirudin, like other anticoagulants, should be used with caution in conditions with increased risks of haemorrhage such as major surgery, biopsy or puncture of a non-compressible vessel within the last month; a history of haemorrhagic stroke, intracranial or intraocular bleeding including diabetic (haemorrhagic) retinopathy; a cerebral ischaemic attack within the last 6 months, a known haemostatic disorder (congenital or acquired, e.g. haemophilia, liver disease) or a history of gastrointestinal or pulmonary bleeding within the past 3 months.

Precautions:

When desirudin is administered in patients with increased risk of bleeding complications, mild to moderate hepatic dysfunction and/or mild to moderate renal impairment aPTT should be monitored and peak aPTT should not exceed twice the control value. If necessary, therapy with desirudin should be interrupted until aPTT returns to less than two times the control value at which time treatment with desirudin can be resumed at a reduced rate.

Desirudin should be used with care in patients receiving anticoagulants, and/or platelet inhibitors, and/or non-steroidal anti-inflammatory medicinal products. Monitoring for evidence of bleeding is advised (see Interactions). The concomitant use of desirudin with thrombolytics and ticlopidine has been investigated in this patient population.

The anticoagulant effect of desirudin is poorly reversible. aPTT levels can, however, be reduced by intravenous administration of DDAVP (desmopressin).

Antibodies/re-exposure: Antibodies have been reported in patients treated with hirudins. Potential for cross-sensitivity to hirudin products cannot be excluded. Fatal anaphylactic/anaphylactoid reactions have been reported with hirudin product therapy. Hirudin-specific IgE evaluations may not be indicative of sensitivity to desirudin as this test was not always positive in the presence of symptoms.

Laboratory Tests:

Activated partial thromboplastin time (aPTT) should be monitored in patients with increased risk of bleeding and/or renal or hepatic impairment. Peak aPTT should not exceed twice the control value. If necessary, therapy with desirudin should be interrupted until aPTT falls to less than twice the control

at which time treatment with desirudin can be resumed at a reduced dose (see also Interaction with other medicinal products and other forms of interactions).

Use during Pregnancy and Lactation:

Category B3

Desirudin is contraindicated during pregnancy, i.e. pregnancy must be excluded and a pregnancy test performed in women of childbearing age. Birth defects in animal experiments, characterised by spina bifida in rabbits and omphalocele in rats, were seen at doses comparable to or above the human therapeutic dose range and were causally related to the administration of desirudin.

It is not known whether desirudin is excreted in human milk. However, lactating mothers should be advised to avoid breast feeding or alternative drugs used.

Effects on Ability to Drive and Use Machines

Unknown

Interaction with Other Medicinal Products and Other Forms of Interaction

Any agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of desirudin therapy. If co-administration cannot be avoided, close clinical and laboratory monitoring should be conducted.

During prophylaxis, concomitant medication with heparins (unfractionated and low-molecular weight heparin) and dextrans is not recommended. The effects of desirudin and unfractionated heparins or prolongation of aPTT has been shown to be additive.

As with other anticoagulants desirudin should be used with caution in conjunction with medicinal products which affect platelet function: these medications include systemic salicylates, NSAIDS including ketolorac, acetylsalicylic acid, ticlopidine, dipyridamole, sulfipyrazone, abciximab, clopidogrel and glycoprotein IIb/IIIa antagonists.

Use in Patients Switching from Oral Anticoagulants to Desirudin or from Desirudin to Oral Anticoagulants:

If a patient is switched from oral anticoagulants to desirudin therapy or inversely, the anticoagulant activity should continue to be closely monitored with appropriate methods. That activity should be taken into account in the evaluation of the overall coagulation status of the patient during the switch.

UNDESIRABLE EFFECTS

The nature of orthopaedic operations and the mode of action of the two drugs studied account for most of the adverse experiences reported in controlled clinical trials investigating desirudin 15 mg twice daily and a standard dose of unfractionated heparin. As with other anticoagulants, bleeding is the most common adverse experience.

All adverse experiences irrespective of trial drug relationship and reported with an incidence of more than 1.0 % are by decreasing order of frequency the following: bleeding episodes, nausea, wound secretion, fever, injection site mass, haematomas, anaemia, hypotension, urinary retention, deep thrombophlebitis, hypokalaemia, insomnia, vomiting, hyperpyrexia, constipation, oedema in legs,

urinary tract infection, cystitis, dizziness, haematuria, joint dislocation, pain in legs, pain, dyspnoea, impaired wound healing, hypertension, oliguria.

Other adverse experiences reported with a frequency equal or below 1% included: epistaxis, abdominal and chest pain, confusion, haematemesis, increases in serum transaminases, rash, urticaria.

Allergic reactions have been reported in the same proportion (1.6%) of patients treated with desirudin (N=2367) or with unfractionated heparin (N=1134) in clinical trials, regardless of causality.

Antibodies/Re-exposure:

Antibodies have been reported in patients treated with hirudins. Potential for cross-sensitivity to hirudin products cannot be excluded. Fatal anaphylactic/anaphylactoid reactions have been reported with hirudin product therapy. Hirudin-specific IgE evaluations may not be indicative of sensitivity to desirudin as this test was not always positive in the presence of symptoms.

In post marketing surveillance, isolated cases of fatal haemorrhage and anaphylactic/anaphylactoid reactions have been reported.

OVERDOSE

There is no antidote for desirudin. Overdosage of desirudin could lead to bleeding complications. In such cases desirudin should be discontinued. If necessary, plasma expanders and/or blood transfusion may be used.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Anticoagulant

Mechanism of Action:

Desirudin is a highly potent and selective inhibitor of free circulating and clot-bound thrombin. A mean peak aPTT prolongation of around 1.4 times baseline value is observed following a subcutaneous twice daily injection of 15 mg desirudin. At therapeutic serum concentrations it has no effect on other enzymes of the haemostatic system such as factors IXa, Xa, kallikrein, plasmin, tPA, or activated protein C. In addition, it does not display any effect on other serine proteases, such as the digestive enzymes trypsin or chymotrypsin, or on complement activation by the classical or alternative pathways.

In two controlled double blind clinical trials, the overall rate of thromboembolic events in patients treated with desirudin 15 mg subcutaneously twice daily, (N=370) was half that in patients treated with a standard dose of unfractionated heparin (N=369) ($p=0.0001$); the rate of proximal deep venous thrombosis was only one fifth that observed with the heparin ($p=0.0001$). To date clinical data are available on hip surgery only.

Pharmacodynamic Effects:

The anticoagulant properties of desirudin are demonstrated by its ability to prolong the clotting time of human or rat plasma whether induced directly (thrombin time) or via the intrinsic (aPTT) or extrinsic (PT) pathways. Desirudin has no profibrinolytic activity.

PHARMACOKINETIC PROPERTIES**Absorption:**

Mean absorption time of subcutaneous (SC) desirudin is 4.1, 4.5, and 5.4 h for dose levels of 0.1, 0.3 and 0.5 mg/kg, respectively (overall mean \square 4.6 h). Absorption is complete based on mean area under the curve (AUC) values.

Following administration of single subcutaneous doses of 0.1-0.75 mg/kg, plasma concentrations of desirudin increased rapidly to maximum levels (C_{max}) between 1 and 3 h. Both C_{max} and AUC values are dose proportional.

Distribution:

Desirudin is distributed in the extracellular space with a distribution volume at steady state of 0.25 l/kg independently of the dose.

Metabolism and Elimination:

The disappearance of desirudin from plasma is rapid in the first phase with approximately 90% of an intravenous (IV) bolus dose disappearing from the circulation within 2 hours of the injection. A slower terminal elimination phase follows with a dose-independent mean terminal elimination half-life of 2 to 3 h. The mean residence times are 1.7-2 h and 6-7 h after IV and SC administration respectively.

The total urinary excretion of unchanged desirudin amounts to 40-50% of the administered dose.

Metabolites lacking one or two C-terminal amino acids constitutes a minor proportion of the material recovered from urine (\square 7%). In vitro and in vivo animal data indicate that desirudin is for the most part eliminated and metabolised by the kidney. Hepatic elimination of desirudin or the thrombin-desirudin complex does not appear to be significant.

Total clearance of desirudin has been found to be in the same range following either SC or IV administration (ca 1.95-2.20 ml/min/kg) and was dose-independent. The total renal clearances of desirudin are slightly reduced in elderly subjects compared to young volunteers. This decrease can be considered unlikely to be of clinical significance, thus allowing no dose reduction.

Preclinical Safety Data

General toxicology studies with a variety of laboratory animal species have not displayed any evidence of target organ or systemic toxicity. Doses were limited by the pharmacological activity of desirudin, which was characterised by bleeding at the sites of injection and in some organs resulting from the inhibition of blood clotting activity. A low grade vasculitis and fibrinoid necrosis were only observed in dogs. These effects were associated with a low and inconsistent presence of antibodies specific to desirudin in the dog and as such they have been attributed to a dog specific immunological reaction. No such antibodies were found in rabbits or baboons.

Reproductive toxicology studies showed desirudin to be teratogenic with changes comprising spina

bifida in rabbits and omphaloceles in rats. No mutagenic potential was demonstrated.

PHARMACEUTICAL PARTICULARS

List of Excipients

Powder for solution for injection: one vial contains magnesium chloride and sodium hydroxide for injections.

Solvent for solution for injection: one solvent ampoule contains mannitol 3% and water for injections.

Incompatibilities

Desirudin should not be mixed/injected with other agents or solvents.

Shelf Life

2 years

After reconstitution: 24 hours at 2-8°C.

Special Precautions for Storage

Protect from light and store below 25°C.

Nature and Content of Container

Dry powder - Colourless glass vial 2 ml, glass type I, with stoppers made from butyl rubber covered with a fluoropolymer film on the product side.

Solvent - Colourless glass ampoule 1 ml, hydrolytic glass type I.

Instructions for Use and Handling, and Disposal

To prepare the reconstituted aqueous solution, 0.5 ml of the accompanying mannitol ampoule is added under aseptic conditions to the vial containing the dry substance. The drug is rapidly redispersed by shaking gently. The reconstituted solution should be used as soon as possible. It is, however, stable for 24 hours in the refrigerator (2 - 8°C); after this period, the reconstituted solution should be discarded.

Do not use reconstituted vials containing visible particles.

Medicine Classification

Prescription Medicine

Package Quantities

Cartons containing 10 vials of dry powder (desirudin, 15 mg) and 10 ampoules of solvent (mannitol solution, 3%).

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