

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Revasc 15mg/0.5ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15 mg desirudin.

After reconstitution one vial contains 15 mg** desirudin* per 0.5 ml

Desirudin consists in a single chain polypeptide of 65 amino acid residues and 3 disulphide bridges.

* produced by recombinant DNA technology in yeast cells.

** 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 alpha-thrombin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White powder and clear, colourless solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of deep venous thrombosis in patients undergoing elective hip or knee replacement surgery.

4.2 Posology and method of administration

Treatment with Revasc should be initiated under the guidance of a physician with experience in coagulation disorders. Instructions for the preparation of Revasc are provided in section 6.6.

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 days up 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, preferably at an abdominal site. Injections should be rotated between at least four different sites.

Children

There is no experience in children.

Patients with renal impairment

Desirudin is contraindicated in patients with severe renal impairment (creatinine clearance of less than 30ml/min corresponding to a serum creatinine > 2.5mg/dl or 221µmol/l; see section 4.3). In

patients with mild or moderate renal impairment (creatinine clearance between 31 and 90 ml/min; see section 4.4) activated partial thromboplastin time (aPTT) should be monitored.

Patients with liver impairment

Desirudin is contraindicated in severe hepatic impairment (see section 4.3). In patients with mild to moderate liver impairment (see section 4.4) aPTT monitoring is recommended.

4.3 Contraindications

Desirudin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients
- with active bleeding and/or irreversible coagulation disorders
- with severe renal and hepatic impairment
- during pregnancy (see section 4.6)
- with severe uncontrolled hypertension and subacute bacterial endocarditis.

4.4 Special warnings and precautions for use

Warnings

Anaphylaxis: Revasc may cause allergic reactions including anaphylaxis and shock (see section 4.8). Fatal anaphylactic reactions have been reported in patients re-exposed to hirudin product therapy in a second or subsequent treatment course. Although fatal reactions have not been reported with desirudin, alternative treatment options must be considered before the decision to re-expose a patient to Revasc. As these reactions are immune-mediated, patients with previous exposure to hirudin or hirudin analogue may be at an increased risk. Treatment initiation with Revasc should be undertaken only in a setting where medical assistance is readily available and where there is access to treatment for anaphylactic reactions. Patients should be informed that they have received Revasc.

Desirudin should not be administered by intramuscular injection owing to the risk of local haematoma.

Desirudin 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 twice the control value at which time treatment with desirudin can be resumed at a reduced dose.

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 section 4.5). The concomitant use of desirudin with thrombolytics and ticlopidine has not 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).

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 section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Any agent which may enhance the risk of haemorrhage should be discontinued prior to initiation of desirudin therapy. If co-administration cannot be avoided, close clinical and laboratory monitoring should be conducted (see section 4.4).

During prophylaxis, concomitant use of medicinal products containing heparins (unfractionated and low-molecular weight heparins) and dextrans is not recommended. The effects of desirudin and unfractionated heparins on prolongation of aPTT have been shown to be additive (see section 4.4).

As with other anticoagulants desirudin should be used with caution in conjunction with medicinal products which affect platelet function these medicinal products include: acetylsalicylic acid and NSAIDs, ticlopidine and clopidogrel, glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) and iloprost.

If a patient is switched from oral anticoagulants to desirudin therapy or from desirudin to oral anticoagulants, 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 (see section 4.2).

4.6 Pregnancy and lactation

There are no adequate data from the use of desirudin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Revasc is contraindicated in pregnancy (see section 4.3). It is not known whether desirudin is excreted in human milk. However, lactating mothers should be advised to avoid breast feeding or alternative medicinal products used.

4.7 Effects on ability to drive and use machines

Revasc has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In controlled clinical trials investigating desirudin 15 mg twice daily and a standard dose of unfractionated heparin, the nature of the hip surgery operation and the mode of action of the two drugs studied account for most of the adverse experiences reported. As with other anticoagulants, bleeding is the most common adverse reaction.

The following related adverse reactions were listed below by system organ class and within each frequency grouping, adverse reactions are presented in order of decreasing seriousness: common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1,000$).

Investigations

Uncommon: Increase in serum transaminases

Blood and the lymphatic system disorders

Common: Anaemia

Nervous system disorders

Uncommon: Dizziness, insomnia, confusion

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Gastrointestinal disorders

Common: Nausea

Uncommon: Haematemesis, vomiting, constipation

Renal and urinary disorders

Uncommon: Haematuria, urinary retention

Skin and subcutaneous tissue disorders

Uncommon: Rash, urticaria

Metabolism and nutrition disorders

Uncommon: Hypokalaemia

Infections and infestations

Uncommon: Urinary tract infection, cystitis

Injury, poisoning and procedural complications

Common: Wound secretion

Uncommon: Impaired wound healing

Vascular disorders

Common: Hypotension, deep thrombophlebitis

Uncommon: Epistaxis, hypertension

General disorders and administration site conditions

Common: Fever, injection site mass, haematomas, oedema in legs

Uncommon: Pain in legs, pain, abdominal and chest pain

Immune system disorders

Common: Allergic reactions have been reported in the same proportion (1.6%) of patients treated with desirudin (N=2,367) or with unfractionated heparin (N=1,134) in clinical trials, regardless of causality.

Rare: Anti-hirudin antibodies have been detected upon re-exposure to desirudin in clinical trials.

Adverse reactions irrespective of trial drug relationship reported during clinical trials were bleeding episodes, oliguria, hyperpyrexia and joint dislocation.

In post-marketing surveillance, rare reports of major haemorrhages, some of which were fatal; and rare reports of non-fatal anaphylactic or anaphylactoid reactions leading to shock have been received.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticoagulant, ATC code: B01AE01

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 (SC) b.i.d. injection of 15mg 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 15mg s.c. b.i.d. (N=370) was half that in patients treated with a standard dose of unfractionated heparin (N=396) ($p < 0.0001$); 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.

5.2 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 = 4.6 h). Absorption is complete based on mean area under the curve (AUC) values.

Following administration of single SC 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 0.251/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 constitute a minor proportion of the material recovered from urine (<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 1.95-2.20ml/min/kg) and was dose-independent. The total and 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 requiring no dose reduction.

5.3 Preclinical safety data

Reproductive toxicology studies in animals showed desirudin to be teratogenic with changes comprising *spina bifida* in rabbits and omphaloceles in rats. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: magnesium chloride
sodium hydroxide
Solvent: mannitol (E 421)
water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C when reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the vial and ampoule in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

15mg of powder in a vial (Type I glass) with stopper (butyl rubber) covered with a film (fluoropolymer) in the product side and 0.5ml of solvent in an ampoule (Type I glass).

Pack size of 1, 2 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

To prepare the reconstituted aqueous solution, 0.5ml of the accompanying mannitol solvent is added under aseptic conditions to the vial containing the powder for solution for injection. The active substance is rapidly redispersed by shaking gently producing a clear solution.

The reconstituted solution should be used as soon as possible (see section 6.3 above).

Any unused product or waste material should be disposed in accordance with local requirements.

Do not use reconstituted vials containing visible particles.

7. MARKETING AUTHORISATION HOLDER

Canyon Pharmaceuticals Limited
7th Floor
52-54 Gracechurch Street
London EC3V 0EH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/043/001	2 vials/2 ampoules of solvent
EU/1/97/043/002	10 vials/10 ampoules of solvent
EU/1/97/043/003	1 vial/1 ampoule of solvent

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 July 1997

Date of latest renewal: 9 July 2007

10. DATE OF REVISION OF THE TEXT

ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURING AUTHORISATION
HOLDER RESPONSIBLE FOR BATCH RELEASE**

B. CONDITIONS OF THE MARKETING AUTHORISATION

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim RCV GmbH & Co KG (BI RCV)
Dr. Boehringer Gasse 5 - 11
1121 Vienna
Austria

Name and address of the manufacturer responsible for batch release

Canyon Pharmaceuticals GmbH
Unter Gereuth 10
D-79353 Bahlingen a.K.
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON
THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: FOR 2 VIALS (15mg/vial) AND 2 AMPOULES

1. NAME OF THE MEDICINAL PRODUCT

Revasc 15mg/0.5ml powder and solvent for solution for injection
Desirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15mg desirudin with 18,000 ATU/mg corresponding to approximately 270,000 ATU per vial.

3. LIST OF EXCIPIENTS

Powder: magnesium chloride, sodium hydroxide
Solvent: mannitol, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
15mg of powder in a vial and 0.5ml of solvent in an ampoule

Pack size of 2

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute immediately before use with solvent provided. Read the package leaflet before use.

Subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution, immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours between 2°C and 8°C (in a refrigerator).

Keep the vial and ampoule in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Canyon Pharmaceuticals Limited
7th Floor
52-54 Gracechurch Street
London EC3V 0EH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/043/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: FOR 10 VIALS (15mg/vial) AND 10 AMPOULES

1. NAME OF THE MEDICINAL PRODUCT

Revasc 15mg/0.5ml powder and solvent for solution for injection
Desirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15mg desirudin with 18,000 ATU/mg corresponding to approximately 270,000 ATU per vial.

3. LIST OF EXCIPIENTS

Powder: magnesium chloride, sodium hydroxide
Solvent: mannitol, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
15mg of powder in a vial and 0.5ml of solvent in an ampoule

Pack size of 10

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute immediately before use with solvent provided. Read the package leaflet before use.

Subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution, immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours between 2°C and 8°C (in a refrigerator).

Keep the vial and ampoule in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Canyon Pharmaceuticals Limited
7th Floor
52-54 Gracechurch Street
London EC3V 0EH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/043/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: FOR 1 VIAL (15mg/vial) AND 1 AMPOULE

1. NAME OF THE MEDICINAL PRODUCT

Revasc 15mg/0.5ml powder and solvent for solution for injection
Desirudin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15mg desirudin with 18,000 ATU/mg corresponding to approximately 270,000 ATU per vial.

3. LIST OF EXCIPIENTS

Powder: magnesium chloride, sodium hydroxide
Solvent: mannitol, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
15mg of powder in a vial and 0.5ml of solvent in an ampoule

Pack size of 1

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute immediately before use with solvent provided. Read the package leaflet before use.

Subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

After reconstitution, immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours between 2°C and 8°C (in a refrigerator).

Keep the vial and ampoule in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Canyon Pharmaceuticals Limited
7th Floor
52-54 Gracechurch Street
London EC3V 0EH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/043/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL: 15mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Revasc 15 mg/0.5 ml
Powder for injection
Desirudin
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15mg of desirudin

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL: 0.5ml SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Revasc 15 mg/ 0.5ml
Solvent for parenteral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5ml of water for injections with 3% (w/v) of mannitol

Medicinal product no longer authorised

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Revasc 15mg/0.5ml powder and solvent for solution for injection

Desirudin

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or your pharmacist.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Revasc is and what it is used for
2. Before you use Revasc
3. How to use Revasc
4. Possible side effects
5. How to store Revasc
6. Further information

1. WHAT REVASC IS AND WHAT IT IS USED FOR

The common name of the active substance in Revasc is desirudin. Desirudin is a recombinant DNA product derived from yeast cells. Desirudin belongs to a group of medicines called anticoagulants, which prevent blood clots from forming in the blood vessels.

Revasc is used to prevent blood clotting after elective hip or knee replacement surgery, as harmful blood clots can form in the blood vessels of the legs. It is often given for several days after operations because blood clots are most likely to form when you are resting in bed.

2. BEFORE YOU USE REVASC

You must not be given Revasc

- if you are hypersensitive (allergic) to natural or synthetic hirudin, including desirudin or any of the other ingredients of Revasc
- if you are bleeding a lot or have any serious bleeding disorder (e.g. haemophilia)
- if you have serious kidney or liver disease
- if you have a heart infection
- if you have an uncontrolled high blood pressure
- if you are pregnant.

Take special care with Revasc

Make sure you tell your doctor if you are likely to have an increased risk of bleeding, which may be the case if you have, or have had:

- bleeding disorders or a family history of bleeding disorder
- stomach ulcers or any other bleeding disease of the gut
- history of a stroke, or bleeding within the brain or eye
- a recent operation (including dental surgery) or biopsy or pricking of a blood vessel within the last month
- recently a brief shortage of blood supply to a part of the brain within the last six months

- bleeding in the gut or lung within the past three months.

Your risk of bleeding may also be increased:

- if you have recently given birth, fallen, or suffered a blow to the body or head
- if you are already taking medicines, especially blood-thinners (see below).

If any of the above apply to you, the doctor or nurse will monitor your blood for clotting activity and may change your dose or dosing schedule accordingly.

Cross-sensitivity to other hirudin products is possible. You should also inform your doctor if you have ever received Revasc, hirudin or an hirudin analogue.

Children

There is no experience with Revasc in children.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It may be necessary to change the dose, to take other precautions, or in some cases to stop taking one of the medicines. This applies to both prescription and non-prescription medicines, especially:

- medicines used to prevent blood-clotting (warfarin, heparin and dicoumarol)
- medicines which affect the function of platelets (particles in the blood involved in blood-clotting), e.g. acetylsalicylic acid, a substance present in many medicinal products used to relieve pain and lower fever, and other non-steroidal anti-inflammatory agents.

Pregnancy and breast-feeding

You should not be given Revasc if you are pregnant. Revasc can cause serious harm to your baby. It is therefore important to tell your doctor if you are pregnant or planning to become pregnant. If you are of a child-bearing age, a pregnancy test may be done by your doctor to make sure you are not pregnant.

It is advisable not to breast-feed during treatment.

3. HOW TO USE REVASC

You will be given Revasc as an injection under the skin.

Administration is by subcutaneous injection, preferably at an abdominal site. Injections should be rotated between at least four different sites. 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 mobile, whichever occurs first. Currently, there is no clinical experience to support the use of Revasc beyond 12 days.

Usual dosage

Always take Revasc exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual dosage is 15mg injected twice a day for 9 days to a maximum of 12 days. You will be given the first injection within 5 to 15 minutes before the operation. If you need treatment for longer than 12 days, the doctor may switch you to another similar medicine.

If you have a kidney or liver disease, the doctor or nurse will monitor your blood for clotting activity and may change your dose or dosing schedule accordingly.

If you are given more than you should

Overdose with Revasc may lead to bleeding. If this occurs, Revasc will be stopped and treatment given for the bleeding.

If a dose is missed

If a dose of this medicine is missed, it should be given to you as soon as possible. If it is almost time for the next dose you will skip the missed dose and go back to the normal dosage schedule. The dose should not be doubled.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Revasc can cause side effects, although not everybody gets them. Some of these side effects may be similar to the effects of surgery. The most likely side effect is bleeding.

Tell the doctor or nurse as soon as possible if any of the following side effects occur, some of which may be confused with side effects of surgery:

Common reported side effects (likely to affect between 1 in 10 and 1 in 100 patients):

Unusual tiredness or weakness (anaemia), nausea, oozing of fluid from wounds, low blood pressure, fever, inflammation of veins sometimes accompanied by a clot, lumps at injection sites, bruising, swelling of the legs caused by fluid retention, non-fatal allergic reactions.

Uncommon side effects (likely to affect between 1 in 100 and 1 in 1,000 patients):

Increase in liver enzymes, dizziness, sleeplessness, confusion, feeling breathless, vomiting (with or without blood), constipation, blood in your urine, difficulty in urinating, rash, itching (urticaria), low levels of potassium in the blood, burning feeling when passing urine with also an increased frequency of urination, slow healing of wounds, nose bleeds, high blood pressure, pain (including pain in legs, stomach and/or chest).

Rare side effects (likely to affect between 1 in 1,000 and 1 in 10,000 patients):

Anti-hirudin antibodies have been detected upon re-exposure

Isolated cases of fatal bleeding have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE REVASC

Keep out of the reach and sight of children.

Do not use Revasc after the expiry date which is stated on the carton and the pack.

Do not store above 25°C. Keep the vial and ampoule in the outer carton.

After reconstitution, immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours between 2°C and 8°C (in a refrigerator).

Do not use Revasc if you notice that the solution for injection contains visible particles.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Revasc contains

The active substance is desirudin (15mg/0.5ml powder).

The other ingredients in the powder are magnesium chloride and sodium hydroxide. In the solvent the ingredients are mannitol and water.

Important information about some of the ingredients of Revasc

This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 ml, i.e. essentially 'sodium-free'.

What Revasc looks like and contents of the pack

Revasc consists of a vial containing a white powder and an ampoule containing clear, colourless solvent for solution for injection.

Pack sizes: 1 vial and 1 ampoule in one package
2 vials and 2 ampoules in one package
10 vials and 10 ampoules in one package

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is:

Canyon Pharmaceuticals Limited
7th Floor
52-54 Gracechurch Street
London EC3V 0EH
United Kingdom

The manufacturer is:

Canyon Pharmaceuticals GmbH
Unter Gereuth 10
D-79353 Bahlingen a.K.
Germany

This leaflet was last approved on.