SCIENTIFIC DISCUSSION

This module reflects the initital scientific discussion and scientific discussion on procedures, which have been finalised before 1 February 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are common complications of orthopaedic surgery and other major surgery. The principal factors leading to DVT are believed to be thrombin generation during surgery, stasis and vein wall injury. The most widely used anticoagulant is heparin, which is often used in combination with other pharmacological or mechanical methods to enhance efficacy in high-risk patients. Thus, there is considerable scope for improvement of the existing preventive therapies for DVT and PE.

Desirudin is a synthetic analogue of hirudin, manufactured by recombinant DNA technology, using a yeast vector. Hirudin is a natural anticoagulant found in the saliva of the European leech (Hirudo medicinalis). Desirudin is a single-chain polypeptide consisting of 65 amino acids containing 3 disulphide bridges. It is nearly identical in structure and amino acid sequence to the natural anticoagulant hirudin with the exception that it lacks a sulphate group on amino acid Tyr 63.

The therapeutic indication claimed for desirudin is: "Prevention of deep venous thrombosis in patients undergoing elective hip or knee replacement surgery". The recommended dose is 15 mg twice daily post-operatively by subcutaneous injection for 9-12 days or until the patient is fully ambulant.

Desirudin has been found to be an active, specific and selective thrombin inhibitor, which offers pharmacological advantages over other anticoagulants:

- it does not require antithrombin III to exert its effect
- it can inactivate clot-bound as well as free thrombin
- it has no direct pro-aggregatory effects on platelets
- it is unlikely to be inactivated by anti-heparin proteins

For these reasons, desirudin has been selected for development in prophylaxis against postoperative thromboembolic complications.

2. Chemical, pharmaceutical, and biological aspects

Composition of the medicinal product

The pharmaceutical form of Revasc (15 mg) is a " is presented as powder and solvent for solution for injection".

The active substance of Revasc is is presented as 15 mg of desirudin (15 mg) presented as a lyophilised powder in vials. The excipient is for Revasc includes magnesium chloride present as a stabiliser (after lyophilisation). The pH is adjusted to 7.4 with a solution of sodium hydroxide. There is an overage of 5% to enable withdrawal of 15 mg of desirudin after reconstitution with 0.5 ml mannitol solution. The containers for the lyophilised powder areis 2 mla colourless, hydrolytic glass, type I Eur.Ph. vials with butyl rubber stoppers covered with a fluoropolymer film on the product side.

Each solvent ampoule contains 15 mg of mannitol in 0.5 ml water for injection (pyrogen free) strength. The solvent has an overage of 20%. The solvent ampoules are 1 ml colourless glass of 1 ml volume, hydrolytic glass, type I Eur.Ph.

Method of preparation

The active substance is manufactured by NOVARTIS, (formerly Ciba Geigy), Basel, and Switzerland.

Three different methods have been used in the production of desirudin. The two earlier methods suffered from low yields and degradation at the C-terminus of the desirudin by host cell carboxypeptidase activity during fermentation and purification. The current method III, using a yeast host strain TR 1456, demonstrated better yields, less degradation and an improved impurity profile. utilising a yeast host strain TR 1456.

A production batch of desirudin has been defined as the amount of active ingredient obtained from 3 consecutive fermentation batches, which have been partially purified separately. They are pooled and subject to further purification as a single batch.

The manufacturing procedure for Revasc 15 mg vials involves standard pharmaceutical procedures summarised in several steps: preparation of solution, adjustment of pH-value, sterile filtration (as terminal steam sterilisation is not possible), filling, prestoppering with sterilised stoppers, lyophilisation, insertion of stoppers, securing with aluminium caps and visual inspection.

Adequate tests are described for in-process controls during manufactureformulation of the product.

During the review of the product dossier, Ciba requested a transfer of the manufacture of the finished product and the diluent from Ciba-Geigy Stein, Basle, Switzerland to Dr. Madaus GmbH, Germany.

In the manufacturing process carried out in Dr. Madaus' plant, the following modifications have been made: an increase in the batch size (from 40,000 to 60,000 vials*),* pre-filtration prior to sterile filtration, steam sterilisation of the stoppers and the shortening of the primary drying phase in the lyophilisation cycle.

One batch of Revasc lyophilisate 17/389/4 has been manufactured in the Madaus facility and meets the specifications. The process will be validated by further batches and the complete validation report will be available by May 1997.

The manufacturing process for the diluent has 2 minor changes: a decrease of the batch size from 115,000 to 80,000 ampoules and the filtration of the solution during the ampoule filling in a continuous process.

The modifications to the manufacturing process, carried out during the review procedure, are deemed to have no discernible effect on the quality of the product and, as such, are acceptable.

Control of starting materials

Each production batch of the active substance is tested according to the specifications for: identity (i.e. description, SDS gel electrophoresis, amino acid sequence and peptide mapping), purity (isoelectric point, clarity, pH, water content and absorbance at 420 nm, sulphated ash, heavy metals, dimmer and related substances, yeast proteins, DNA, microbial contamination and bacterial endotoxines) and potency (protein content and biological activity per mg).

During the evaluation of the dossier the company has summarised and re-examined the related substances limits and has agreed to tighten them following further manufacturing experience. Data provided on the revised limits are acceptable. The active substance specifications have been amended in order to reflect all changes requested by the CPMP during the assessment process. These amendments include limits for ammonium, CGP 51 013 and CGP 51 012, other related substances and total dimmer content.

Development genetics

Desirudin is produced in Saccharomyces cerevisiae strain 1454 transformed with expression plasmid pDP34/GAPFL-YHIR. A single yeast transformant is used for subsequent master and working cell banks. Its coding sequence was synthesised chemically using the known aminoacid sequence of hirudin variant I (HVI) from the leech *Hirudo medicinalis* and includeding the signal sequence of the yeast acid phosphatase (PH05). The expression of desirudin in yeast is controlled by the GAPFL promoter ligated to the coding sequence of the PH05 signal sequence., whereas Tthe 1.1 kb expression cassette was cloned into the high copy number yeast vector pDP34.

The signal sequence targets the newly synthesised protein (desirudin) to the endoplasmic reticulum where, on entry to the lumen, a peptidase cleaves the signal sequence and the desirudin is then secreted into the culture broth. The mature desirudin is secreted into the culture broth after cleavage of

the signal sequence by the entry of a peptidase to the lumen.All the elements required for the expression and secretion of desirudin in S. cerevisiae have been described adequately and a diagram of the expression cassette has been included by the Company.

A detailed description of the shuttle vector pDP34 has been provided. Satisfactory details of characterisation are given up to, and beyond, the normal population doubling level to be used in full scale production. The Company has adequately characterised the plasmid by restriction mapping and DNA sequence analysis to monitor its structural stability.

The applicant has argued that the repeated isolation of single yeast colonies and routine checking of the strain's auxotrophic markers and its specific protease deficiencies rule out microbial contamination.

Preparation and description of master cell bank (MCB) and working cell bank (WCB)

The preparation and validation of the master cell bank (comprising 50 vials stable for at least 5 years in liquid nitrogen) is adequately described. Full details of the validation tests have been submitted. The production of the WCB represents 8 doublings in relation to the MCB. Sufficient number of WCB vials has been produced to sustain a production campaign for 1-2 years.

A sample of WCB vials is Quality Control tested to the MCB specification before being released for use in production. The Company provided additional satisfactory clarification of the Quality Control test regarding proof of absence of fungal contamination.

Fermentation

In process parameters are adequately described and the manufacturing site of the active substance appears to be in compliance with GMP regulations.

During the review procedure, the Company, following a CPMP request, replaced meat peptone with soya in the fermentation medium.

The Company has produced 2 validation batches 00796 and 00896 with this new medium. Product from these batches has been compared with product from bovine derived peptone fermentation. The results of the peptide mapping, microheterogenicity, amino acids sequencing, physio-chemical analyses etc, demonstrate that the active ingredient is identical in both cases.

These batches were put on a stability programme in December 1996.

Purification

The description of the purification process is comprehensive. It consists of 9 stages leading to the active substance. The host cell proteins and other impurities of higher and lower molecular weights are removed by gGel filtration during this process. The applicant has tabulated further data for the in-process limits for down stream processing and the results of the validation batches.

Active substance characterisation

The active ingredient (CGP 39393) and related substances (CGP51012 and CGP 51013) can be detected by HPLC. A wide range of studies of high quality has been presented to confirm the structure of desirudin. It has been characterised by amino acid composition, location of disulphide bonds, N and C terminal amino acid sequence analysiswere studied, confirmationevidence of primary and secondary structure, (by peptide mapping and digestion with S. aureus protease), and elucidation of tertiary structure (by NMR in solution and by X-Ray Crystallography).

The biological, immunological and physico-chemical characterisation of the product was performed using several techniques. Desirudin has an isoelectric point of 3.8 -4.3, is highly soluble in aqueous solution and has an elementary composition as expected.is reported

The specific biological activity of desirudinCGP 39393 is approximately 18 000 antithrombin units (ATU) per mg of desirudin with reference to the WHO Second International Standard for α-thrombin(12.000 ± 1500 antithrombin units (ATU) mg determined by the useof the 1st international std of thrombin) is comparable to the activity of highly purified authentic hirudin. . The HPLC content

is ~ 92%. This estimation of biological activity is based on the inhibition of thrombin-induced fibrinogen aggregation with the assessment of the strength of the resulting gel. The company indicates in the SPC that the specific activity is an approximate value.The tests used during analytical development have been adequately described and validated.

Further details submitted by the Company demonstrated the consistency of production and the purification process. Satisfactory data regarding improvement of the reproducibility of the SDS gel electrophoresis is used as an identification test was provided.
The active ingredient specification has been updated (PW-367H2) to take into account all requested changes, which arose throughout the assessment.

Control of the finished medicinal product

The proposed specifications and control methods for the finished product are mainly based on tests and limits defined for the active ingredient. These methods have been validated.

During the assessment procedure, the Company was asked to clarify aspects such as the proposed limit for "visible foreign particles", test for magnesium, test for bacterial endotoxins and sterility compliance with the Ph. Eur. Other points for clarification concerned pH and endotoxin limits for the diluent. The company still is requested to address post-authorisation a validation report on the batches used in the manufacturing proces at Dr. Madaus GmbH, Germany and to amend the specification for the foreign particles test.

The applicant has provided a new edition of the Ciba Monograph (PD-860H2) taking into account all requested changes.

A validation report on the manufacturing batches produced at Dr. Madaus GmbH, Germany will be submitted in May 1997.

Stability

Stability of active ingredient

The stability of desirudin was examined under normal and accelerated storage conditions (temperature, light [200,000 Lux for 1 day] and 75% relative humidity) and under normal storage conditions. The results obtained showed that the proposed storage conditions of ≤ 8 °C, protected from light, humidity and microbial contamination with a retest period of 18 months is justified.

Stability of the finished product

Data provided on 3 batches of the final formulation (F. 4) showed good stability i.e. product remaining within specification under normal storage conditions (8°C and 25°C) for up to 24 months.

Updated stability data have been supplied and support a 24-month shelf life for the finished product (6 batchesmonths of bovine derived active ingredient). Batches 00796 and 00896, using the soya derived peptone, were placed on stability trials in December 1996. The results from these ongoing trials will be available by the end of 1997.

The proposed shelf life of 24 months is justified on the basis of the satisfactory additional data provided by the applicant. However, the appropriate shelf life for the proposed marketing formulation of the solvent is only 18 months as data are limited to this time period. A common expirye date of 18 months is therefore considered necessary for Revasc powder and the mannitol solvent. A variation to extend the shelf life can be made when further satisfactory data become available.

The reconstituted solution should be used as soon as possible after preparation. It has been demonstrated, however, to be stable for 24 hours when stored in a refrigerator (2-8° C); after this period, the reconstituted solution should be discarded.

Inspection status

In June 1995, the applicant requested the following manufacturing sites to be considered when the dossier was submitted:

Manufacturer of the active substance:

Former Ciba-Geigy Ltd (now called NOVARTIS), Klybeckstrasse 141, Ch-4002 Basel, Switzerland.

Manufacturer of the finished product and storage of the finished product:

Ciba-Geigy Ltd,Ch 4332 Stein, Switzerland.

Manufacturer responsible for batch release and import in the EEA:

Ciba Pharmaceuticals, Wimblehurst Road, Horsham, West Sussex RH12 4AB, UK.

In February 1996, following the inspection report of the manufacturing site of the active substance and finished product, the applicant was notified of failures to comply with GMP in Stein, Switzerland.

In November 1996, the company requested to transfer the site of change of manufactureing site responsible for the finished product from Stein in Switzerland to Dr. Madaus, Germany and the manufacturer responsible for batch release from Horsham in UK toin Ciba, Huningue, France.

In January 1997, following the amended administrative part IA for the manufacturing sites, the applicant provided a timetable for validation of the transfer from Ciba-Stein to Dr. Madaus and a description of the manufacturing process (updated part IIB) for the finished product. Clarification of some points arisingen from the assessment of the additional pharmaceutical and biological data were verified during the inspection. The German Authorities in a product related inspection during 17 and 18 of February 1997 inspected the facilities of Dr. Madaus and a satisfactory report was issued on 13 March 1997.

3. Toxico-pharmacological aspects

Desirudin was shown to be a specific and potent inhibitor of human thrombin and inactivates both free and fibrin-bound thrombin. The following pharmacological and toxicological studies have been carried out and detailed in Part III of the dossier.

Pharmacodynamics

The anticoagulant potential and mechanism of action of desirudin have been explored in vitro, *ex-vivo* and *in vivo* and desirudin is found to affect both primary haemostasis (platelet aggregation) and secondary haemostasis (fibrin generation). The pre-clinical data are confirmed in the clinical section, where convincing inhibition of platelet aggregation is demonstrated in healthy volunteers.

Primary haemostasis studies showed that thrombin-induced platelet aggregation was inhibited by desirudin at an A_2 value of 0.003 µM, the corresponding value for platelet activating-factor-induced aggregation was >0.55 µM, and for collagen was > 5.5 µM.

In secondary haemostasis, prothrombin time (PT), thrombin time (TT) and activated partial thromboplastin time (APTT) were assessed in vitro as indices of anticoagulation by studying the inhibition of $CaCl_2$ generated thrombosis in platelet-free plasma. APTT was shown to be of intermediate sensitivity and gave an approximately linear response at concentrations of desirudin from 0.01 to 0.1 µM, therefore, it was adopted for the animal studies.

Desirudin was found to be a potent and specific inhibitor of both the intrinsic and extrinsic coagulation cascade, with a K_i of the order of 0.0002 µM. In vivo studies using several animal models of hypercoagulability have shown prolongation of APTT.

Desirudin was shown to have no significant effect on other enzymes involved in the process of haemostasis, or on other serine protease enzymes such as trypsin or chymotrypsin, or on complement activation by the classical or alternative pathways.

General (secondary) pharmacodynamic studies were limited to an investigation of cardiovascular and respiratory parameters in cats and guinea pigs and no significant findings were observed.

Limited preclinical data are available regarding drug interactions but this issue has been studied in humans and, therefore, no further animal work is necessary.

Pharmacokinetics

The pharmacokinetic behaviour of desirudin was comparable in the animal species used in toxicity tests (rat, dog, cynomolgus monkeys) and in humans.

Absorption

The absolute bioavailability of desirudin in the rat, after a dose of 5.5 mg/kg (subcutaneous administration) was approximately 83%. The mean residence time (MRT) of desirudin for rat, dog and man is 0.49, 0.78 and 1.55hr respectively and is similar to the half-life reported in the published literature. Dose proportionality has been convincingly demonstrated in rat and dog, although there appear to be minor divergences from strict proportionality in the monkey.

Distribution in normal and pregnant animals

There is little tissue uptake. That which does occur is predominantly by the kidney, with levels in other organs at or below the threshold of detection. There is transfer to the foetus, in the rabbit, at concentrations of 0.015 to 0.1% of the dose administered. It is not known whether transfer in milk occurs.

Metabolism

In the intact rat, no unchanged desirudin was found after administration of a 30-mg/kg dose. The occurrence of metabolites, in the isolated perfused rat kidney, indicates intrinsic capacity for renal metabolism of desirudin in this species. The rat liver is also found to be metabolically active, with the kidney having a 100 fold greater capacity than the liver. In the dog, it is thought that the disappearance of 26-36% of the administered dose may have represented metabolism and sequestration, possibly in the renal tube. Neither liver nor kidney was metabolically active in any other species studied.

Elimination

Desirudin is rapidly eliminated, with an overall half-life in the region of 1-2 hrs in all species. It's clearance is predominantly or totally renal, based on the observation that the plasma clearance coincides with the glomerular filtration rate.

Toxicology

Single dose toxicity

Single dose intravenous studies were conducted in rats, mice, monkeys and dogs. No major bleeding episodes were observed at the doses employed. The findings were limited to those expected from the pharmacological activity of the drug.

Repeated dose toxicity

Repeated dose toxicity studies up to 3 months duration were conducted in rats (s.c route) and dogs (i.v route). In addition, toxicity studies with drug administration by continuous i.v infusion were conducted in dogs (7 days treatment duration) and cynomolgus monkeys (14 days treatment duration). The findings in species other than the dog were limited to enhanced pharmacological effects (its intended anticoagulant effect). Serious bleeding seems to occur at doses above 5 mg/kg, as a very rough approximation the recommended human therapeutic dose is 15 mg 12 hourly i.e. 0.25 mg/kg for a 60 kg patient, or 0.5 mg/kg if calculated on a daily rather than a 12 hourly basis.

No target organ or unexpected systemic toxicity was identified except in the 3-month dog i.v study, where vasculitis and fibrinoid necrosis of the vessel wall in numerous organs and tissues were observed in 5 animals (at 10-25 mg/kg). The frequency and severity of this event were shown to be greater in the treated than in the control groups: it was considered to be related to the immunogenic response to desirudin as 16/19 of the dogs tested had high titres of anti-desirudin antibodies. Desirudin was present in plasma both in free form and in a form of high molecular mass, which was identified as antibody complex based on its behaviour on a gel filtration column. The elimination half-life of the antibody complex was estimated to be >20 hours. The antibodies formed against desirudin did not appear to have neutralising activity, as the antibody complex inhibited blood coagulation. The occurrence of vasculitis and antibodies observed in the dog is referred to in the SPC under pre-clinical information.

Immunogenicity

Studies of the species specificity of desirudin antigenicity were carried out. Animals were given low dose i.v exposure, followed by a booster exposure, a regimen likely to generate hypersensitivity. Desirudin specific antibody formation and skin test responses to an interdermal injection of desirudin were evaluated. In the dog, skin tests were negative. In the rabbit both antibodies and skin responses were negative. In the baboon skin test responses were negative and antibody formation was not documented. In man, low levels of antibodies have been recorded in some subjects and very high levels in one subject exhibiting urticaria after exposure.

Reproduction studies

There was no evidence of adverse effects on general reproductive performance, fertility, or postnatal development in rats given desirudin by s.c injection. The highest dose administered (10 mg/kg) was limited by the pharmacological effect of desirudin.

Four developmental toxicity studies were conducted (two in the rat by the s.c route and two in the rabbit by the i.v route), all complied with GLP. Desirudin was considered to be teratogenic in rats (low incidence of omphaloceole and incomplete closure of the abdominal wall) and rabbits (spina bifida, malrotated limbs, cranial changes and gastroschisis).

Mutagenic potential

A complete battery of genotoxicity tests was carried out. There was no evidence of mutagenic activity in three in vitro assays (bacterial mutation test, in vitro gene mutation assay in Chinese hamster V79 cells, in vitro cytogenetic assay in Chinese hamster ovary cells). The results of an in vivo assay (rat micronucleus) were also negative. All studies were conducted according to satisfactory protocols, using GLP.

Carcinogenic potential

Carcinogenicity studies have not been conducted and are not required for the proposed clinical indication.

Local tolerance

A 5 day subcutaneous local tolerance study in rabbits comparing formulations containing calcium chloride and magnesium chloride showed that the latter (the proposed clinical formulation) was better tolerated. Microscopic changes of minimal fibrosis and haemorrhage were similar to those seen with desirudin alone.

No ecotoxicity studies have been carried out with desirudin. This does not appear to be necessary for this recombinant protein product which has no unusual peptide bonds or amino acid residues and which will undergo enzyme proteolysis by microorganisms in waste water systems. Neither the active substance desirudin nor the excipients present an environmental risk and no further data are required.

It is concluded that the studies reported in Part III of the dossier are appropriate and support the marketing authorisation application for this product.

4. Clinical aspects

The standards used in the conduct of the clinical studies were considered to be good and those after 1991 were conducted according to the CPMP standards of GCP.

The following assay methods were used in the pharmacodynamic and pharmacokinetic studies:

- Enzyme-Linked Immunosorbent Assay (ELISA); used to determine desirudin in plasma and urine, and also to recognise the thrombin-desirudin complex.
- High Performance Liquid Chromatography (HPLC); used to determine desirudin in urine.
- Thrombin Chromogenic Assay (TCA); measures the inhibitory activity of desirudin containing fluids on exogenous thrombin.

Human pharmacology (Phase I studies)

The human pharmacology of desirudin was investigated in 445 subjects, mainly healthy volunteers. Both i.v and s.c dosing regimens were used ranging from 0.1-1.0 mg/kg; s.c dosing regimens for up to 6 days and i.v up to 72 h were included. The recommended dose of 15 mg is equivalent to 0.2 mg/kg for a 70 kg, or 0.3 mg/kg for a 50 kg patient.

- Pharmacodynamics. The activated partial thromboplastin time (APTT) gave a linear response at plasma concentrations of desirudin from 0.01 to 1mM and is used to monitor therapy. Thrombin time is too sensitive to be useful as a monitoring test. Plasma levels of desirudin (by ELISA) are closely related to biological effect. Desirudin has no clinically significant effect on platelet count or on the bleeding time.
- Pharmacokinetics. Bioavailability after s.c administration is 100% that of the i.v route. Kinetics are dose dependent and excretion is primarily renal. Although in the healthy elderly the bioavailability was somewhat greater than in the young, this does not translate into a greater pharmacodynamic effect, and is therefore unlikely to be of clinical significance. With moderate to severe renal impairment (GFR<31/mL/min) patients studied showed that there is increasing pharmacodynamic activity with decreasing renal function. Patients with hepatic impairment have not been studied. The proposal by the applicant to contraindicate desirudin in patients with severe hepatic impairment and to monitor APTT in patients with lesser degrees of hepatic impairment is considered satisfactory.
- Interaction studies. The potential for interaction between desirudin and warfarin was evaluated in a three-day study in healthy volunteers, anticoagulation had not stabilised by the end of the study. No interaction was seen with aspirin and piroxicam. The ability of desmopressin to reverse anticoagulation generated by desirudin was tested: although a small fall in APTT was observed, desmopressin cannot be considered to reverse the effect of desirudin in a manner which would be therapeutically useful.
- Bioequivalence. The clinical trials of desirudin were conducted using a formulation known as F1. In order to improve stability F4, the market formulation, contains magnesium chloride instead of mannitol. Bioequivalence was demonstrated between F1 and F4 in a study carried out in 12 healthy male volunteers.

Clinical trials (Phases II and III)

In Part IV of the initial dossier, data are provided on 1621 patients included in clinical studies of whom 1120 received desirudin and 501 unfractionated heparin. Five hundred and nineteen patients received the recommended dose of 15 mg.

During the evaluation of the dossier additional data from a multicentre double blind comparative study were provided in order to compare desirudin to enoxaparin - a low molecular weight heparin.

In the clinical studies diagnosis of DVT was by ascending phlebography 4-12 days post-operatively, or earlier if there were clinical signs. Pulmonary embolism (PE) was confirmed by ventilation/ perfusion scanning or pulmonary angiography. The majority of the patients entered into the trials were over 60 years of age. Women of child bearing potential were excluded (entry was restricted to post menopausal females or those who had hysterectomy or tubal ligation). This is because desirudin is teratogenic in two animal species.

Comments on efficacy:

- Study RH/PT3; an open, pilot, dose ranging clinical trial: desirudin at a dose of 15 mg was effective in the prevention of DVT after elective hip replacement and more so than standard doses of unfractionated heparin.
- Study RH/E23; a pivotal study which involves both dose ranging (3 doses of desirudin) and comparator elements (i.e. unfractionated heparin). The conclusion drawn from the trial was that all doses of desirudin were superior to heparin and that the 15 mg and 20 mg doses of desirudin were equivalent.

- Study RH/E 28; a heparin controlled comparator trial similar to RH/E23 but omitting the dose ranging arm. The results confirm those of RH/E23; again desirudin was significantly more effective.
- Study RH/E 25; a multicentre double blind study comparative with enoxaparin. Efficacy was demonstrated in reducing the frequency of major thrombotic events (death, proximal DVT, or pulmonary embolism -PE). The results significantly confirm the efficacy in the primary criterion ($p<0.02$) and the second criterion ($p<0.01$), respectively.

Comments on safety:

Desirudin was well tolerated by healthy subjects (n=445) during the Phase I clinical development.

Three subjects had reactions, which might have been allergic responses; in one case the subject developed urticaria in close temporal relationship to the administration of desirudin.

The overall incidence of recorded adverse events in patients treated for the proposed indication was similar to that found in patients studied in other indications (PTCA and acute myocardial infarction). In cardiac indications at the time of submission, four out of 1247 patients experienced adverse cerebrovascular events in clinical trials, none were haemorragic.

In the indication prophylaxis of thromboembolism-orthopaedic surgery the safety database relates to 1120 patients treated with desirudin and 501 comparator patients treated with heparin. The overall adverse event rate was 65.5% for desirudin and 65.3% for heparin. The studies provided by the company, RH/E 23, RH/E 28 and RH/E 25 showed very similar results for haemorrhagic complications for desirudin, unfractionated heparin and enoxaparin. It seems likely that relatively minor bleeding episodes such as injection site and wound haematoma are commoner with desirudin. At the dosage regimens used in clinical studies, desirudin did not induce major haemorrhagic complications.

The applicant provided additional safety information of desirudin in comparison to low molecular weight heparin. Data showed that adverse experiences were noted in 71% of patients in both treatment groups and, in general, had similar severity. Three patients on desirudin and two on enoxaparin had an allergic reaction, considered to be treatment related.

Minor bleeding episodes, such as haematoma, were more common in desirudin treated patients. Injection site haematoma was also more frequent in desirudin treated patients 29(2.8%) than in enoxaparin patients 6(0.6%). The frequency and quantity of blood loss and tranfusion requirements are both equivalent between treatment groups.

The company has satisfactorily addressed the following issues related to Part IV of the initial dossier during the assessment of the product. The coadministration of coumarin in prophylaxis of venous thromboembolism; the potential for interaction with ticlopidine and the potential of desirudin to cause thrombocytopenia; immunogenic potential and second exposure; the dose suitability according to body weight and the duration of treatment. The SPC was revised accordingly.

The clinical studies in support of the application were conducted solely in patients undergoing elective hip replacement surgery. The CPMP considered, on the basis of the applicant's reasoned argument, that the risk benefit profile in the hip replacement studies was likely to be similar to that for elective knee replacement, and has consequently accepted that therapeutic indication.

5. Conclusion

The applicant has demonstrated that desirudin is more effective than both unfractionated heparin and enoxaparin in the prophylaxis of thromboembolic disease after orthopaedic surgery. Bleeding was slightly more frequent and slightly more profuse than with the comparative products. The risk benefit balance in the proposed clinical indication is considered to be favourable.

6. Post-Authorisation

In post marketing surveillance, rare reports of major haemorrhages, some of which were fatal, and anaphylactic/anaphylactoid reactions leading to shock have been reported.

Anaphylactic reactions
Following a review of the safety database triggered by recently reported severe and fatal anaphylactic/oid reactions with a similar hirudin analogue, the MAH identified cases of possible anaphylactic shock occurring in close temporal association with the use of desirudin. Given that these reactions are immune-mediated, patients with previous exposure to hirudin or a hirudin analogue may be at an increased risk. Consequently, the SPC has been update to reflect these findings. Alternative treatment options must be considered before the decision to re-expose a patient to Revasc. Treatment with Revasc should be initiated under the guidance of a physician with experienced coagulation disorders and 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.