SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 1 August 2003. For scientific information on procedures after this date please refer to module 8B.

I Introduction

Refludan contains Lepirudin ([Leu^1-Thr^2]-63-desulfohirudin) as the active substance. Lepirudin is a hirudin analogue produced in yeast cells transfected with an expression vector containing the hirudin gene.

Refludan is presented as a powder to be reconstituted with water for injection or with isotonic saline for intravenous injection or infusion. It is supplied in one strength with a standardised content of 50 mg lepirudin per vial. The specific activity of lepirudin is approximately 16,000 (Antithrombin Units) ATU per mg, where one ATU is the amount of hirudin that neutralises one unit of the WHO preparation of thrombin (89/588).

Lepirudin is a specific direct inhibitor of free and clot-bound thrombin and the proposed therapeutic indication is anticoagulation in adult patients with heparin-associated thrombocytopenia (HAT) type II and thromboembolic disease mandating parenteral antithrombotic therapy.

HAT type II is a complication of heparin therapy, with a probable incidence of the order of 1% of heparin-treated patients. The disorder is characterised by, sometimes profound, thrombocytopenia and a high propensity for venous and arterial thromboembolic complications occurring during continued heparin treatment. Mortality and amputation rates of 20-30% and 10-20%, respectively, are cited in the more recent literature reviews. The chief underlying pathogenic mechanism seems to be a formation of antibodies directed mainly against a complex of heparin and Platelet Factor 4. These antibodies crossreact with low-molecular-weight heparins and frequently also with available heparinoids. Through binding to the platelet Fc receptor and to heparin-like structures in the vascular endothelium, the antibodies induce platelet activation and endothelial damage, leading to a prothrombotic state.

The serious prognosis for patients with HAT type II and the current lack of therapy with established efficacy, support the need for new therapeutic agents for this thromboembolic complication.

II Overview of Part II of the dossier: chemical, pharmaceutical, and biological aspects

Composition of the medicinal product:

Refludan is presented in 50 mg glass vials containing the active substance lepirudin. The excipients are D(-)-Mannitol (Ph Eur, USP), which is a bulking and tonicity agent, and sodium hydroxide (Ph Eur) for pH adjustment.

The containers are colourless 2mL glass vials (Ph Eur) closed with grey rubber stoppers (Ph Eur) and sealed with aluminium crimp caps. The stoppers and the crimps are protected by plastic flip-off tabs.

Refludan is provided as a lyophilised powder which has to be reconstituted in saline or water for injection prior to administration. The package to be marketed does not contain diluent.

Method of preparation:

Each batch of Refludan is produced from a single batch of purified drug concentrate (PDC). The manufacture of the finished dosage form is performed at ambient temperature and consists of stirring and pH adjustment after the addition of mannitol to the PDC, and sterile filtration.

Adequate tests are utilised for in-process control during formulation of the product. A test for bioburden is performed prior to sterile filtration.

Validation of the process

The procedures employed for sterile filtration of the final bulk solution, the lyophilisation and the filling of vials are satisfactorily validated. The programs adapted for validation and revalidation of the Manufacturing and Shipment Department are considered acceptable.

Control of starting materials

Specifications and routine tests of the active substance

Each production batch of the active substance (PDC) is tested according to the specifications for:

1. identity i.e. RP-HPLC, amino acid composition and peptide mapping .
2. purity
   a) clarity, coloration and pH, which are tested according to Ph Eur.
   b) amount of lepirudin-related proteins
   c) yeast proteins and
   d) microbial contamination (Ph Eur.) and bacterial endotoxines (LAL)
3. evaluation of potency; content of lepirudin , activityand the specific activity.

All non Ph Eur methods have been satisfactorily validated and the specifications according to which the tests are performed are justified by batch data.

Development genetics

Hirudin polypeptide was originally isolated from the leech *Hirudin medicinalis*. The amino acid sequence was determined and used as a template in the design of the synthetic lepirudin gene. The synthetic lepirudin gene was cloned a plasmid. The lepirudin expression vector is transfected into *Saccharomyces cerevisiae* strain.

Standard techniques were applied for the construction of the expression vector and the cloned sequences have been satisfactorily verified. The integrity of the expression vector is confirmed by restriction enzyme mapping and nucleotide sequence analysis at the level of the master and the working seed. The transfected cells are shown to be genetically stable and no significant change in cell viability, plasmid retention or lepirudin yield could be seen after 5 years of storage over liquid nitrogen. Moreover, transfected yeast cells show the same phenotypic characteristics as the host strain.

Cell Bank System

The historic development, preparation and validation of the cell bank system are reported in detail. The consistency of the fermentation process has been shown for a time period which well exceeds the time period used in production.

Production

. Each fermentation run starts from one cryo-vial of the working cell bank. The fermentation is carried out in a closed system and is described briefly in four steps; preparation of the seed culture, pre-fermentation, fermentation and harvesting of the yeast cells.

Basic purification.

At harvest, yeast cells are separated by filtration. Proteolytic enzymes are inactivated. The filtrate is subsequently subjected to chromatography. The eluate is concentrated, acidified and desalted using serial dia- /ultrafiltration steps.

To ensure an acceptable microbial status, tests for biobuden are performed at each step during the basic purification. Acceptable alarm limits for these tests have been established and batches that exceed an alarm limit will be discarded.

Final purification

Upon arrival, the product is further purified by severalchromatographic steps, followed by an ultra-/diafiltration step.

Relevant in-process controls are applied throughout the partition process. Raw materials used during the process are specified and found acceptable. Methods used for sanitation/sterilisation of materials and equipment as well as for regeneration of columns are approved.

To minimise the risk for accumulation of related proteins during purification, storage of intermediates may only be performed under refrigerated conditions and for defined time periods. Furthermore, prior to processing through the final purification steps the crude product is tested for compliance with intermediate specifications which include a limit for the maximum content of related proteins.

Characterisation

A wide range of studies of high quality have been presented to confirm the lepirudin structure. To obtain evidence for the primary and secondary structure, the amino acid composition, amino acid sequence, molecular, peptide map, and the protein profiles in HPLC and HPCE were analysed. Localisation of disulphide bonds were studied. By-products resulting from post-translational events were identified and characterised.

The biological, immunological and physico-chemical characterisation of the product was performed using several techniques.

The anticoagulant activity of lepirudin as well as of the different by-products was determined by analysis of their antithrombin activity. A principal SOP for re-calibration of substandards is currently under preparation and will be submitted as a post licensing commitment.

Data provided demonstrate the consistency of production and the purification process.

Control test on the finished product

The specifications and routine tests have been provided. With regard to the purity, identity and potency of the active ingredient basically the same specifications are applied at release as are applied for control of the PDC. The one exception is that, at the end of shelf-life, more relaxed limits for the sum of related proteins are accepted. The higher levels of related proteins have, however, also been identified in batches used in clinical trials.

A test and a specification for the maximum content of aggregates is included. In addition, appropriate release tests are performed for control of the formulated product such as clarity of solution, coloration, dissolution time and content of excipients.

Stability

Studies on the stability of the active ingredient and the finished product were designed to comply with ICH guidelines. Full time data from the real time studies are not yet available from all batches analysed, but data so far submitted is consistent with a shelf-life for the active ingredient of 18 months at -20° C and for the finished product for 24 month at room temperature. However, data to prove the stability over the entire shelf-life should be submitted on an ongoing basis.

Manufacturing plants and Inspection status

During the assessment of this dossier the applicant requested to add Roussel Uclaf, France as an additional site responsible for the fermentation and the basic purification steps of the manufacture of the active substance. The CPMP requested an inspection. This inspection took place in June 1996, the inspection report provided by the Agence de Medicaments was satisfactory for the manufacturing (dated on 24 July 1996).

The final purification and the batch release of Refludan takes place in Behringwerke AG, Germany. The Manufacturing Authorisation was issued on 31 July 1995 by Regierungspräsidium, Gießen, Germany, and is also satisfactory.

III Overview of Part III of the dossier: toxico-pharmacological aspects

Pharmacodynamics

Aspects of the efficacy and safety of Refludan have been addressed in a large number of animal studies.

Pharmacodynamics

The effects of lepirudin related to the thrombosis inhibitory action have been clearly demonstrated in several animal species, including rat and rabbit venous thrombosis models. An inhibitory action on fibrin formation, and also on platelet function was shown and both are in line with current knowledge on the specific binding of hirudin molecules to thrombin. However, relatively high doses were required to produce an appreciable impact on platelet function. Several in vivo models revealed a preventive action as well as interruption of clot formation, albeit lower dose levels were required to produce the former effect. A much weaker impact on thrombolysis was also shown. Furthermore, the clot inhibitory impact appears to persist longer than for bleeding time prolongation.

Pharmacokinetics

As regards the clearance, an appreciable consistency between the different species subjected to tests of pharmacodynamic action and toxicity of lepirudin, was reported. Renal elimination was predominant. The kidney was identified as the primary site for biotransformation but the enzymatic activity varied between species. A prominent proportion of administered lepirudin was rapidly distributed to the kidneys and the urinary bladder, but some lepirudin-associated activity could also be identified in the liver and lungs. A transient accumulation of considerable amounts in the stomach was also found. In repeat-dose toxicity trials, however, pathology examinations revealed only incidental cases of haemorrhage in kidneys and stomach and these organs do not appear to be at an exceptionally high risk of treatment-related damage.

Toxicology

Safety pharmacology

No acute clinical signs were reported in investigations on secondary pharmacology conducted in rat, cat, dog, rabbit and monkey.

Single- and repeat-dose toxicity trials

In rats, the single-dose and subchronic trials revealed a dose-dependent reaction (catarrh) in the regional lymph nodes, increment of spleen weight as well as anaemia and haemoperitoneum. Moreover, an increased erythropoiesis in bone marrow and spleen was also observed. Some monkeys, subjected to short-term drug exposure, developed uni- and bilateral retinal haemorrhages. In both species, bleedings in various other organs were also reported. With a view to the limited duration of the contemplated human exposure, the most salient findings in animal short-term testing represent the expected outcome from an enhanced pharmacodynamic effect of lepirudin.

In the overall package of toxicity testing, other changes also occurred: Weight increments in the thyroid glands and adrenal glands in drug-exposed animals were reported. Moreover, drug-exposed monkeys, in all repeat-dose trials, showed a tendency towards reduced mean ovary weights and in some of those trials the testes weights were lower in dosed individuals. On the assumption that some these differences could be connected to treatment, they may have a shared aetiology inasmuch as a disturbed pituitary function may cause such actions. However, the changes observed do not represent significant differences in organ weight; the variations within each dosage group were notable and especially marked with respect to the testes and thyroid glands. Since rodents lack thyroxine-binding globulin (TBG), which serves as a thyroid hormone buffer, the rat data may not be best appropriate for risk assessment in human patients. Based on an extended assessment procedure the tendency towards ovary weight change in lepirudin-exposed monkeys, remains as a possible indication of (indirect) gonadal action in this species. However, with a view to the severity of the HAT type II syndrome and thromboembolic disease as well as the limited contemplated drug exposure in humans these findings should not compromise drug safety for the proposed indication.

Antihirudin antibodies were formed during repeated dosing which increased the systemic drug exposure (AUC). An apparent lack of appreciable impact on the pharmacodynamic action indicates a

non-neutralising character of these antibodies. The induction of antihirudin antibodies by lepirudin was not associated with any vascular or renal pathology in animals.

The regional lymph nodes commonly became reddened and enlarged upon exposure to the test substance and quite frequently led to the identification of sinus histiocytosis at this site. This effect was explained by the transport of destroyed erythrocytes to this location. However, lepirudin may also have induced an immunological reaction contributing to, or leading to, hypersensitive reactions.

Local tolerance

The test substance was relatively well tolerated locally, following intravenous administration. However, reactions, such as thickened tissue, oedema and yellowish nodules occurred in some dosed animals. Bleeding at the injection site, after dosing, was a common event. Other routes of administration (s.c., i.a., p.v.) induced a more severe and increased incidence of untoward effects.

Reproduction toxicity and Embryotoxicity/Teratogenicity studies

Low placental transfer of lepirudin was demonstrated. Nevertheless, a developmental study in rabbits showed an embryotoxic action at 30 mg/kg/day. In rats, administered with 30 mg lepirudin/kg (i.v.) in the peri- and postnatal period, the survival of the pups was slightly reduced and the incidence of pups with dilatation of the renal pelvis was increased. The major effect at that dose in rats was an increased maternal mortality during parturition. The proposed SPC statement that Refludan should not be administered to pregnant women or nursing mothers (paragraph 4.6) is appropriate.

Genotoxicity and carcinogenicity

Comprehensive testing showed no mutagenic or clastogenic activity and, recognising the short duration of clinical use, there is no requirement for carcinogenicity data.

Impurities

The batches used in the pivotal toxicity testing have been analysed for their impurity profile. The amount present suggests that the higher doses tested for an exaggerated pharmacodynamic effect/toxicity would have covered any significant effects due to such impurities although more subtle effects would be masked by the toxicity of lepirudin itself.

IV Overview of Part IV of the dossier: clinical aspects

Clinical Pharmacology

A total of 15 pharmacodynamic/pharmacokinetic studies were performed. The studies involved mostly volunteers, but also special groups such as the elderly and patients with impaired renal function. Further pharmacological data were collected in the clinical trials in patients.

Pharmacodynamic studies

Phase I trials showed that lepirudin is a fairly selective thrombin inhibitor and that the activated partial thromboplastin time (aPTT) is a sensitive indicator of its anticoagulant effect. Maximum effect on the aPTT was observed in the first blood sample collected after bolus i.v. administration (0.17h) and at 2 h after s.c. administration and continuous i.v. infusion. The aPTT remained elevated for at least 2 hrs after the end of the infusion, but returned to normal by 24 hours after the start of the infusion. The aPTT is dependent upon the concentration of lepirudin. The lepirudin plasma concentration/aPTT effect relationship is different between healthy volunteers and HAT type II patients; patients exhibit a shallower concentration response curve than do healthy volunteers. However, given that patients have a lower total clearance of lepirudin and achieve higher plasma levels for the same dose, the prolongation of aPTT with respect to dose is similar for healthy volunteers and HAT type II patients.

The initial evaluation of studies in patients with HAT type II gave rise to several questions regarding dose-effect relationships and the usefulness of the aPTT for clinical monitoring. In the responses, the company presented complementary, retrospective analyses that characterised the relationships between plasma lepirudin levels and aPTT ratios, and the relationship between aPTT ratio classes and markers of clinical efficacy and safety. These analyses support the proposed dosage regimen in HAT type II and provide acceptable reassurance that the proposed aPTT ratio of 1.5-3 is associated with the best risk/benefit balance in this patient population.

Lepirudin does not affect platelet counts or bleeding time in healthy subjects. Other potential effects on the coagulation system, as well as any interactions with other drugs, have been only sparingly documented. For the specific therapeutic indication of HAT type II, no further investigations in these areas were considered absolutely essential, however.

Pharmacokinetics studies

The pharmacokinetics of lepirudin following intravenous administration have been well described and were characterised in healthy volunteers, patients with renal impairment, patients with acute myocardial infarction, and, patients with HAT type II.

The analytical assays used to quantify lepirudin in plasma and urine are unspecific in that they quantify all active moieties (lepirudin bioassay, lepirudin ELISA). Lepirudin levels measured by ELISA or bioassay correlate well.

Normal volunteers were studied both after intravenous and subcutaneous administration. The intravenous dosing route is the most relevant to the requested indication and has been studied in three single bolus dose studies at doses from 0.01-0.5 mg/kg, one study using a 6 hour infusion and two multiple dose studies (one q.d. and one b.i.d.). Pharmacokinetic parameters are similar after intravenous and subcutaneous administration.

Lepirudin pharmacokinetics are linear over the range of doses studied. Plasma concentrations returned to baseline 5 hours after single doses. Distribution is confined to the extracellular fluid. Elimination is biphasic, the terminal half life is around 1 hour in healthy volunteers and is independent of dose. Multiple dosing of 0.1mg/kg every 12 or 24 hours for 5 days did not lead to accumulation. Clearance of lepirudin is predominantly renal and between 35-60% of the dose is recovered in the urine during the first 24 hours. Total clearance is closely related to creatinine clearance. In healthy volunteers mean total clearance is approximately 195±45 ml/min and mean renal clearance ranged between 65 to 115 ml/min. In patients with HAT type II, mean total clearance is lower, of the order of 114±48 ml/min. The kidney is also proposed to be the sight of metabolism of the compound since total clearance is almost zero in patients with extreme renal impairment.

In renally impaired but otherwise healthy patients, clearance of lepirudin was decreased and half life was prolonged with increasing degree of renal impairment. Dosage adjustments for HAT type II patients were proposed on the basis of these results obtained in non-cardiovascularly impaired patients. The single major pharmacokinetic concern during the first assessment of the application was that dosage recommendations for renal impairment derived from non-cardiovascularly impaired patients may not be appropriate for patients with HAT type II. The Applicant addressed this question by submitting a population pharmacokinetic analysis of all the studies in which plasma concentrations for lepirudin were available and which showed, indirectly, that the original dosage recommendations are appropriate

Two studies were performed in elderly volunteers, one using the intravenous and one using the subcutaneous route of administration. The pharmacokinetics were altered similarly for both routes studied, with increased exposure as measured by AUC and a longer half life. On the basis of the data provided, it is likely that the pharmacokinetics are more affected by renal function than by age and, thus, there is no need for a dose adjustment in elderly with normal renal function. Clearance is moderately reduced in females and again this difference can be attributed to renal function.

The pharmacokinetic questions have been dealt with satisfactorily.

Clinical Efficacy and Safety

Data from four Phase II trials of lepirudin in other indications (acute myocardial infarction with thrombolysis, acute coronary syndromes and deep venous thrombosis) were included in the dossier and provided information regarding the potential general usefulness of lepirudin as an anticoagulant. The experience gained in these indications was not considered to be immediately relevant to the current application, but it was accepted that the Phase II trials were used by the company to provide guidance for the dosage of lepirudin in patients with HAT type II. This approach was further justified by the complementary analyses of pharmacodynamic data, referred to above.

After submission of additional data, the part of the dossier dealing specifically with clinical experience in patients with HAT type II provided information from two clinical trials (B7 and NR13), involving 198 patients in prospective, noncomparative investigations, and 120 historical patients for comparison. Of the prospectively studied patients, altogether 125 represented the approved target population of HAT type II with thromboembolic disease mandating parenteral antihrombotic therapy. In view of the rarity and clinical severity of the disorder, and since no therapy with documented efficacy has been available, the overall clinical study design was accepted.

Prospectively studied patients

Both clinical trials were executed as multicentre studies. The patients represented a wide spectrum of underlying medical and surgical disorders; their mean age was 58 years and there was a slight female preponderance. Study therapy allocation was to four different groups, according to Table 1.

Table 1: Treatment groups, trials B7 and NR13

Group	No.of patients	Description
A1	114	Patients with acute HAT type II and thromboembolic complications (TEC)
A2	11	Patients with acute HAT type II and TEC who required thrombolytic therapy
B	61	Patients with present or past HAT type II, who required prophylaxis of arterial or venous thromboembolism
C	12	Patients with present or past HAT type II, who required anticoagulation during cardiopulmonary bypass surgery

The diagnosis of acute HAT type II was based on the occurrence of thromboembolic complications (TEC) during heparin therapy (identified in 82% and 86% in trials B7 and NR13, respectively) and on the appearance of a >30% drop in platelet counts or platelet counts <100 G/l during heparin administration (identified in 89% and 75% in trials B7 and NR 13). The presence of thrombocytopenia and/or TEC during heparin therapy was documented in 95% of patients. The diagnosis was further substantiated in all but very few patients by a positive serologic assay, which was almost exclusively the heparin-induced platelet aggregation assay (HIPAA). Patients with (atypically) early-onset thrombocytopenia, or without documented thrombocytopenia, were specifically analysed in complementary data submissions and found to have the same clinical characteristics as those with overtly reduced platelet counts. The diagnosis of HAT type II was, thus, found to be well documented in the presented patient material.

Historical control patients

Altogether 120 evaluable patients were collected from available registries and represented cases diagnosed during the last 10-year period. These patients all had a serologic confirmation of HAT antibodies; approximately 95% had overt thrombocytopenia, while the incidence of TEC attributed to heparin therapy was very similar to that observed in the prospectively studied patients with acute HAT type II. Similar to the prospectively studied patients, they had received a number of theraputic regimens after the diagnosis of HAT type II, including LMWH, heparinoids, oral anticoagulants, aspirin, thrombolytics, and no anticoagulant treatment.

Lepirudin therapy

The intravenous route was used in all treatments. Patients in group A1 received the approved dosage regimen, but the initial bolus dose was omitted for safety reasons in some patients switching directly from other forms of anticoagulant therapy or in an immediately postoperative condition. The median duration of therapy was 10 days. The aPTT was used for monitoring, with the aim to keep values at 1.5-3 times the patient's baseline. A reduced dose was used in patients on concomitant thrombolytic

therapy (group A2), but experience is still too limited to issue definite recommendations in this situation.

Efficacy evaluation

The primary efficacy variable was a composite of adequate anticoagulation and response of thrombocytopenia. Stable anticoagulation within the aPTT ratio window of 1.5-3 was regularly achievable with moderately frequent dose adjustments. As already mentioned, supplementary documentation was provided by the Applicant to characterise the relationship between aPTT ratio and clinical efficacy and safety outcomes. These data showed that the recommended aPTT ratio window was associated with a lower incidence of clinical events than an aPTT ratio <1.5, and that an aPTT ratio >3 did not seem to confer additional clinical benefit. The risk of bleeding increased with increasing aPTT ratio.

Thrombocytopenic patients regularly normalised their platelet counts during lepirudin therapy and no patient developed de novo thrombocytopenia during such treatment. In a complementary analysis of samples from 83 patients, no evidence of cross-reactivity could be found between HAT antibodies and lepirudin.

The clinical efficacy evaluation focused on the incidences during the study period (defined as the treatment period plus two weeks) of new thromboembolic complications (TEC), limb amputations, deaths, and a composite of these. Crude incidences in the target population of acute HAT type II with thromboembolic disease (groups A1 and A2) are given in Table 2, together with a comparison with historical controls.

Table 2: Crude incidences of clinical endpoints, studies B7 and NR13

Event n (%)	**Trial B7 (n=56)**	**Trial NR13 (n=69)**	**Hist. Control (n=120)**	**Comparison B7/NR13 vs hist. control***
Death	3 (5.4%)	8 (11.6%)	21 (18%)	p=0.057
Amputation	2 (3.6%)	5 (7.2%)	8 (6.7%)	p>0.5
New TEC	3 (5.4%)	9 (13%)	30 (25%)	p=0.002
Combined	7 (13%)	18 (26%)	52 (43%)	p=0.001

* Fisher's exact test (2-sided)

In the comparison with historical controls, the two prospective trials taken together showed significant benefit of lepirudin regarding the incidence of new TEC and the combined endpoint, and a trend to benefit regarding survival. There was no discernible effect on the need for amputations, which may largely have been determined by TEC occurring before the start of study therapy. Time-to-event analyses generated similar results, and, overall, the event incidences during lepirudin treatment were low in comparison with published materials on HAT type II. There was no obvious explanation for the, nominal, differences in clinical outcomes between trials B7 and NR13. In both studies, daily event rates were lower during lepirudin therapy than during the period between confirmation of HAT type II and start of lepirudin therapy, or after cessation of this therapy, respectively. There were, however, no indications of a rebound phenomenon with a clustering of TEC immediately after the termination of lepirudin treatment. Mortality was related to underlying disease and no deaths could be attributed to lepirudin therapy.

Safety considerations

The safety data base on the use of lepirudin in patients comprises some 1,000 cases, of whom 198 were patients with HAT type II. The safety problems of lepirudin relate specifically to bleeding and to the antigenicity of the drug. In patients with HAT type II and thromboembolic disease, studied in trials B7 and NR13, the overall incidence of documented bleeds was 39%, very similar between the two studies. In the historical controls, bleedings were documented in 32%. Major bleeding, defined as bleeding demanding transfusion of c2 units, causing a drop in hemoglobin c20 g/l, being overt or demanding surgery or cessation of anticoagulant therapy, was reported in 11% of lepirudin-treated

patients. There were no cases of fatal or intracranial haemorrhage. Documented bleedings were most frequently related to puncture sites and surgical wounds. Haematuria and rectal bleedings were reported in 7% and 3% of patients, respectively. In a regression analysis that compared bleeding events in prospectively studied patients and historical controls, the risk o**f** bleeding was clearly increased with an aPTT ratio >3, compared with the recommended range of 1.5-3. Concomitant thrombolytic therapy and, to a lesser extent, high age were associated with trends to increased bleeding risk with lepirudin, while no obvious influence was seen of sex or type of underlying disease.

In both trials in HAT type II, the formation of specific, IgG-class, anti-hirudin antibodies was recorded in approximately 40% of patients, and follow-up analyses in a limited number of cases showed that positive titres may persist at least up to two years after therapy. Post-marketing, anti-hirudin antibodies have been reported especially with treatment periods exceeding 5 days. Antibodies could not be related to clinical symptoms and there were no observations to suggest that they have neutralising activity. In a few patients, the appearance of antibodies seemed to be related to an enhanced and prolonged effect of lepirudin on aPTT that mandated dose adjustments. A small number of patients with documented positive antibody titres were reexposed to lepirudin during a second course of treatment without untoward effects. Since the experience with reexposure is very limited, it should be undertaken with caution, but in view of the severity of the disorder and the lack of alternative therapy, repeated therapy has not been contraindicated.

The overall incidence of recorded adverse events in patients with HAT type II was similar to that found in patients studied in other indications. The incidences of serious adverse events (SAE's) and of probably lepirudin-associated SAE's were, however, higher in patients with HAT type II than in other studied indications, due mainly to a higher frequency of haemorrages in HAT type II.

5. Conclusions

Acute HAT type II is a clinical emergency, where, so far, no therapy with documented efficacy and tolerability has been available. In the strict sense, the noncomparative design of the performed studies with lepirudin precludes a firm conclusion whether, or, to what extent, lepirudin confers true benefit with respect to the evolution of the disease process in patients with HAT type II. It is, however, the opinion of the Committee that it has been acceptably documented that lepirudin is a clinically usable anticoagulant in adult patients with HAT type II and prevalent thromboembolic disease that mandates parenteral antithrombotic therapy. In view of the severity of the disorder and the current lack of alternative treatment with established efficacy, the Committee recommended a favourable opinion for granting a marketing authorisation for Refludan in this specific indication.

6. Post-Authorisation

Patients with renal impairment

Post-marketing data, mainly arising from a specific Drug Monitoring Programme, indicate a high incidence of severe bleeding events in patients with severe renal impairment, and also that lepirudin was commonly overdosed (compared with the approved posology). The MAH proposed to intensify aPTT-monitoring in patients with bleeding events and impaired renal function (section 4.2), and to strengthen the relevant warning in section 4.4. In the light of these findings, treating physicians should carefully weigh the risk of Refludan administration versus its anticipated benefit. It may be necessary to exclude patients with renal impairment from treatment with lepirudin regimen.

Anaphylactic reactions including fatal shock

Further to the report of 7 cases of typical or suspected acute anaphylactic reaction with immediate onset reaction following re-exposure to Refludan, 5 of which were fatal, an Urgent Safety Procedure procedure was used to implement changes in the product information in an expedited manner. During a subsequent assessment, the MAH identified altogether 26 cases of suspected serious anaphylactic reactions in a cumulative database of approximately 35,000 patients (including clinical trials).

The possibility of introducing a contraindication to repeated exposure to Refludan was rejected in view of the lack of alternatives licensed throughout the EU for this indication. Therefore, the SPC was updated to reflect the Refludan may cause allergic reactions including anaphylaxis and shock, and that fatal anaphylactic reactions have been reported in patients re-exposed to Refludan in a second or subsequent treatment course. Hence, alternative treatment options must be considered before the

decision to re-expose a patient to Refludan. As these reactions are immune-mediated, patients with recent exposure to hirudin or hirudin analogue may be at an increased risk. Treatment initiation with Refludan should be undertaken only in a setting where medical assistance is readily available and where there is access to treatment for anaphylactic reactions, and patients should be informed that they have received Refludan.

The recommendations for use in patients scheduled for a switch to orally administered coumarin derivatives (vitamin K antagonists) have been updated. Thus, coumarin derivatives should be initiated only when platelet counts are normalising. The intended maintenance dose should be started with no loading dose.To avoid prothrombotic effects when initiating coumarin, parenteral anticoagulation should be continued for 4 - 5 days. The parenteral agent can be discontinued when the INR stabilises within the desired target range.