

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of BeneFIX. This scientific discussion has been updated until 1 September 2000. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Haemophilia B is an inherited bleeding disorder characterised by the deficiency in clotting factor IX (FIX), 4 to 8 times less common than haemophilia A. There are less than 10,000 patients with haemophilia B in the US and Europe. The frequency and type of haemorrhages in individuals with haemophilia B depend on the age of the individual and severity of the defect in haemostatic function. Factor IX plays an essential role in both the extrinsic and intrinsic haemostatic pathway. Individuals with “severe” haemophilia B have FIX levels ≤ 1 International Units (IU) per dl. Persons with “moderate” haemophilia B have FIX activity levels of 1 to 5 IU/dl and individuals with “mild” haemophilia B have FIX activity levels of 5 to 30 IU/dl.

Plasma-derived factor IX (pdFIX) products are used routinely to treat patients with this condition. Crude FIX-containing concentrates first became available over 30 years ago. These early preparations had a very low FIX specific activity (< 5 IU/mg) and were designated as prothrombin complex concentrates (PCCs) because they contained factors II, VII, and IX. Early PCCs notably improved quality of life, prolonged life span, and increased socio-economic productivity of patients with haemophilia B.

Use of these products has been associated with hypercoagulable states, thromboembolic diseases, and may adversely affect immune function. The thrombotic complications were manifested clinically as arterial or venous thromboses (including stroke), the development of disseminated intravascular coagulation, pulmonary emboli, and transmural myocardial infarctions in young patients. Clinical studies have confirmed that high-purity plasma-derived products (hp pd factor IX) have markedly diminished thrombogenic potential as compared to crude preparations. Other clinical complications which have occurred with plasma-derived factor replacement therapies have also included isoagglutinin-associated haemolysis, allergic reaction, and inhibitor development.

The use of plasma-derived clotting factors also has resulted in the inadvertent transmission of pathogenic blood-borne viruses. Moreover recent reports of plasma donors diagnosed with Creutzfeldt-Jakob Disease (CJD) have increased the concern of potential contamination by non-conventional agents in the blood supply, although the risk of CJD transmission via plasma-derived products such as FIX has been considered as extremely remote or theoretical by the experts, on the basis of experimental data, and is not supported by any epidemiological evidence.

The methods currently in place to produce high-purity products incorporate stringent criteria for donor selection and steps designed to inactivate or remove multiple lipid-enveloped viruses, such as hepatitis B and C viruses and HIV. Recent methods tend to diminish the persistence of nonlipid encapsulated viruses (non-enveloped virus), such as parvovirus B19 and hepatitis A virus, but still leaving recipients of plasma-derived replacement products potentially vulnerable to the consequence of known and hitherto unknown viruses.

BeneFIX contains, as active substance, 250 IU, 500 IU or 1,000 IU of the recombinant coagulation factor IX (rFIX; INN = nonacog alfa). Nonacog alfa has a primary amino acid sequence that is identical to the Ala¹⁴⁸ allelic form of plasma-derived factor IX [pdFIX], and some post-translational modifications of the recombinant molecule are different from those of the plasma-derived molecule. Recombinant coagulation factor IX is a glycoprotein that is secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHO) cell line. This recombinant factor IX was developed in an attempt to avoid or reduce complications arising during therapy:

In particular, no human or animal proteins are added in the production or formulation of BeneFIX, and therefore it is not contaminated by human blood-borne infectious agents or by other plasma-derived clotting factors (e.g. factors II, VII, and X).

The therapeutic indications of BeneFIX are for control and prevention of haemorrhagic episodes, and for routine and surgical prophylaxis in previously treated patients with haemophilia B (Christmas Disease, i.e. congenital factor IX deficiency). The dosage and duration of the substitution therapy depends on the severity of the factor IX deficiency, on the location and extent of the bleeding episode, on age and clinical condition of the patient and on factor IX recovery. Estimation of the required dosage of rFIX can be based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity, on an average, by 0.7 IU/dl. However, pharmacokinetics have to be assessed regularly in each patient and posology has to be adjusted accordingly.

2. Overview of chemical, pharmaceutical, and biological aspects

BeneFIX is supplied as a sterile, non-pyrogenic, lyophilised cake for reconstitution with Sterile Water for Injections (SWFI), presented in glass vials with rubber stoppers.

It is a single-use product for intravenous administration. The finished product contains neither preservative nor added animal or human components.

It is available in three dosage strengths (250 IU, 500 IU and 1,000 IU per vial). The powder is to be reconstituted with either 5 ml (250 IU and 500 IU) or 10 ml (1,000 IU) water for injection. The vial containing the solvent (sterile water for injections, SWFI) is supplied, with the vial of powder, in the final package.

After reconstitution with the appropriate volume of solvent, the rFIX concentration in the finished product is either 100 IU/ml (500 IU and 1000 IU presentation) or 50 IU/ml (250 IU presentation). The vials contain a slight excess of rFIX to assure withdrawal and administration of the labelled amount. The lyophilised powder for injection is produced from a pH 6.8 solution containing rFIX (ca. 110 IU/ml), 10 mM L-histidine, 260 mM glycine, 1% sucrose and 0.005% polysorbate 80.

Excipients meet the Eur. Pharmacopoeia Standards.

The methods used for the preparation of the finished product are widely described, and the process validation performed is fully acceptable. Compatibility of the formulation with the container and closure system has been assessed through development studies as well as through the formal stability program. The consistency of the manufacturing process can be considered demonstrated.

The manufacturing process as well as the analytical developments has been extensively validated, thus providing good batch-to-batch consistency of the process. Taking together the in-process controls performed and final specifications set up, assurance is provided in terms of production of a consistent product of high quality.

GMP compliance of the manufacturing process has been assessed with the relevant GMP inspections. On the basis of the experience gained in stability studies, the storage conditions proposed for the active ingredient are considered acceptable.

The final product, rFIX, is a very complex, highly post-translational modified molecule. The recombinant protein has been characterised in detail and structural differences with respect to post-translational modifications have been assessed in comparison to pdFIX.

rFIX is not identical to pdFIX, as there are some differences in post-translational modifications. The MAH will perform the testing as required but considered specific testing procedures to be confidential in nature and therefore asked the paragraph to be deleted: the Rapporteur's experts agreed

Assays for the release of lyophilised rFIX drug product are performed on each lot to determine identity, purity, potency, and safety.

The rFIX drug product stability program has been designed in accordance with ICH guidelines. Lots of lyophilised rFIX drug product of each of the 250-IU and 1000-IU dosage forms have been placed on long-term stability at 2 to 8° C and on accelerated stability at 25° C, 60% relative humidity, and at 40° C, 75% relative humidity, thereby bracketing the 500-IU dosage form which has the identical formulation, stopper, and glass type.

The stability of rFIX drug product is being assessed via a subset of the release assays.

A container-closure integrity test is also being performed annually at 12, 24, and 36 months for all lots on long-term and accelerated stability.

rFIX drug product has been stored at 2 to 8° C for 36 months and at 25° C, at 60% relative humidity for 12 months. All assays indicate that rFIX drug product is stable and has shown no significant change with respect to identity, strength, quality, and purity. The approved shelf life is 36 months at 2-8° C.

For the purpose of ambulatory use the product may be removed from such storage for one single period of maximum 1 month at room temperature (up to 25°C). At the end of this period, the product should not be put back in the refrigerator.

As follow-up measures, the company will address minor points for clarifications as well as additional information on the manufacturing process. The data has been assessed at the annual re-evaluation of the dossier.

3. Overview of toxico-pharmacological aspects

Toxicology

BeneFIX has been evaluated in toxicology studies performed in different animal species for periods of 1 day to 28 days. No indications of systemic toxicity were seen in two species at intravenous doses as high as 200 IU/kg. Intraperitoneal doses of 500 to 2500 IU/kg in the mouse indicated activation of coagulation as determined by the presence of widespread thrombosis and clinical laboratory evidence of consumptive coagulopathy, and all adverse effects in the animals were related to these. Similar effects have been described in the same species treated with pdFIX preparations.

Time and dose-dependent antibody development was seen. Adverse clinical signs observed were consistent with mild anaphylaxis and correlated with development of anti-FIX antibodies. This immunological response of the animals to a human protein, limit the value of the repeated dose studies performed with respect to the pharmacokinetic parameters.

Mutagenicity

rFIX was evaluated for mutagenic potential in the Ames assay with and without metabolic activation assay measuring chromosome aberrations in human blood lymphocytes. No evidence of mutagenicity was observed in these two in vitro tests.

No reproductive, developmental or carcinogenicity studies have been done for rFIX. These omissions have been noted in the SPC.

Pharmacodynamics

The in vitro and in vivo pharmacology studies focused on the canine model of haemophilia B as a relevant model of efficacy for the human factor IX deficiency. The results indicate that rFIX restores the clotting defect in factor IX-deficient canine plasma and improves haemostasis in the genetic model of factor IX deficiency. In addition, evaluation in a modified Wessler Stasis model has shown rFIX to have low thrombogenicity.

Pharmacokinetic

Pharmacokinetic parameters of rFIX have been determined after single and multiple intravenous doses in different species. The PK parameter estimates were linear across all doses evaluated (40 to 200 IU/kg), and accumulation of rFIX was not found. The PK parameters obtained in studies comparing rFIX to pdFIX were similar to those obtained in human studies with respect to maximum FIX concentrations, distribution and elimination half-lives and clearance and show a 30% lower recovery of rFIX in comparison to pdFIX. The lower recovery of rFIX in comparison to pdFIX may be due to different post-translational modifications compared to pdFIX.

Clinical aspects

The clinical trials submitted in support of the Marketing Authorisation application were planned in accordance with the CPMP guideline (at that stage in draft) for evaluation of plasma derived factor IX concentrates with regard to patient numbers, pharmacokinetic and laboratory evaluations and surgeries performed. However these guidelines can only be taken as a minimum recommendation, especially because they are not intended to cover the development of recombinant DNA coagulation factors.

Four clinical studies provided data presented in the dossier to support the MAH application, three carried out in PTPs and one in PUPs.

Patients with various degrees of severity of the disease (most suffering of a severe form) were enrolled from 15 participating centres in the United States (N = 11) and in Europe (N = 4).

The clinical experience, provided to support the Marketing Authorisation application, referred to 2333 cumulative exposure days (median of 37 days) for 693 bleeding episodes and many prophylaxis infusions. Forty-four PTPs and 33 PUPs were enrolled.

This overview is now updated with the post-authorisation experience.

Pharmacokinetics

Information known pre-authorisation

Data on PK were provided by studies designed in agreement with the EU guideline for pdFIX. The pharmacokinetic parameter estimates for rFIX were consistent across all studies involving previously treated patients.

In the crossover pharmacokinetic evaluation of rFIX and a pdFIX in PTPs (n = 11), infusion of rFIX into patients with haemophilia B resulted in in-vivo recoveries of 38 ± 14 %.

The plasma half-life of rFIX was 18.1 ± 5.1 hours.

The PK crossover comparison study of rFIX and a pdFIX indicated that the elimination half-lives were nearly identical (17.7 ± 5.3 hrs for the pdFIX) whereas the in-vivo recoveries were statistically different (53 ± 12 % for the pdFIX).

The observed mean 0.75 IU/dl rise in rFIX activity per IU/kg of rFIX administered was at the lower end of the range of what is known for plasma-derived human coagulation factor IX concentrates.

The lower extent of sulfation and lack of phosphorylation of rFIX may account for the 30% lower recovery of BeneFIX compared to pdFIX. Individual adjustment of posology to clinical response may be needed as mentioned in the SPC.

Post-authorisation update

The *in vivo* recovery is lower than expected from the first clinical studies. Infusion of BeneFIX into 56 patients with haemophilia B has shown an *in vivo* recovery ranging from 15 to 62% (mean 33.7 +/- 10.3%). One International Unit of BeneFIX showed a mean 0.75 IU/dL (range 0.3 to 1.4 IU/dL)

increase in the circulating level of factor IX. The biologic half-life ranged from 11 to 36 hours (mean of 19.3 +/- 5.0 hours). A 30% lower recovery of rFIX in comparison to pdFIX was shown.

The SPC was amended accordingly through a type II variation. The new wording included revised information on posology, pharmacokinetics and adverse reactions, including cases of severe anaphylaxis. A positive opinion was adopted by the CPMP on 23 July 1998. The Commission Decision amending the Marketing Authorisation was adopted on 11 November 1998.

Clinical Efficacy

A) Previously Treated Patients (PTPs) and PTPs in surgery

Information known pre-authorisation

Data on safety and efficacy of rFIX in previously treated patients (PTPs) with moderate or severe haemophilia B were obtained from the study C9417-21 and treatment of bleeding intra- and post-operatively from the surgical segments of the 2 studies C9407-21 and C9408-21 if they were to undergo any major or minor elective surgical procedures that required factor IX replacement therapy. The studies C9407-21 and C9408-21 consisted of three segments: an open-label, baseline pharmacokinetic evaluation of rFIX followed by replacement treatment appropriate for each individual patient.

Treatment allowed on-demand therapy identical to that of the second segment of C9407-21 and routine secondary prophylaxis for patient who had been on such a prophylactic regimen for at least 6 months.

Clinical efficacy was assessed in several ways:

- response per infusion for bleeding episodes was assessed subjectively and reported according to a four-point scale (“excellent”, “good”, “moderate”, and “no response”);
- in the surgical setting, efficacy parameters in addition to response included estimated total blood loss during and after the procedure and any blood transfusion requirement;
- to prevent haemorrhages, intermittent prophylaxis (prophylaxis given to prevent haemorrhages during particularly active days -e.g., before sports or exercise, or to facilitate healing of a “target joint”) was assessed by evaluating the objective data regarding the presence or absence of a spontaneous musculoskeletal bleeding episode or the resolution of the target joint or both;
- routine prophylaxis was assessed every 3 months or when a change of regimen was necessary according to a three-point scale of “excellent” (no spontaneous musculoskeletal bleeding episodes), “effective” (reduced number of spontaneous musculoskeletal bleeding episodes during prophylactic regimen), and “inadequate” (change in prophylactic regimen necessary).

Failure of rFIX to control or prevent bleeding episodes was defined as follows:

- lack of response in controlling bleeding episodes (on-demand treatment): No response after two successive infusions within 24 hours for the same haemorrhage in the absence of confounding factors attributable to the bleeding episode or clinical condition of the patient;
- failure of rFIX in prophylaxis: Occurrence of a spontaneous musculoskeletal bleeding episode within 48 hours of a prophylactic infusion of rFIX on two or more occasions in the absence of other confounding factors (e.g., trauma, injury, incorrect dose).

Of the 693 haemorrhages treated, 566 (82%) resolved after a single infusion of BeneFIX. Out of 972 infusions, 815 (84%) infusions were rated to have good/excellent responses. Moderate responses were reported for 139 infusions (14%). Fifteen infusions could not be rated because the site of bleeding was unknown or could not be compared to previous episodes. Three infusions for 3 separate haemorrhages did not provide any response.

The study results of rFIX used for on-demand treatment, for prophylaxis, and during surgery in these patients, all demonstrate that rFIX shows an overall favourable efficacy profile. Several patients,

however, had spontaneous breakthrough bleedings despite prophylaxis possibly due to insufficient trough levels of factor IX activity.

There was a trend towards the need of increased doses which is in accordance with the results of the pharmacokinetic evaluations. Patients undergoing surgeries were treated successfully with rFIX.

The need for an increased dosage of BeneFIX is not fully explained. During the clinical studies the dosing of BeneFIX increased in several patients for the treatment of bleeding episodes or prophylaxis. Genetics Institute, the MAH at the time, was asked to provide precise statistics on the relation between the dosage and the clinical response in all patients enrolled in the studies.

Post-authorisation update

The amount of BeneFIX to be infused, as well as the frequency of infusion, varies with the patient and clinical situation. At the time of the grant of the Marketing Authorisation, the clinical data indicated that estimation of the required dose of BeneFIX could be based on the empirical finding that one unit of factor IX activity per kilogram of body weight was expected to increase the circulation level of factor IX on an average by 0.8 IU/dl. Information submitted at the time of the first periodic safety update report (PSUR) indicates that the average increase in circulating factor IX is 0.7 IU/dl (range from 0.3 to 1.4 IU/dl).

At the time of the first PSUR, 57 PTPs have been enrolled in the PTP studies C9407-21 and C9408-21. Five patients have withdrawn their consent to participate in the studies. Twenty-one patients have completed the study and 31 patients are attending follow-up visits. Nine of the 52 patients showed alterations in pharmacokinetic parameters or increase in FIX consumption. The trend towards an increase of dose or frequency of rFIX treatment, already noted at the time of the grant of the Marketing Authorisation, is still ongoing and remains unexplained.

In the data available in support of the application for a Marketing Authorisation, 73% of the doses administered were less than 50 IU/kg. The update provided with the first PSUR showed that 57% of patients increased their doses. Due to recovery or to obtain sufficient therapeutic response or both, thirty-six out of fifty two PTPs have received doses higher than 50 IU/kg. Therefore, close monitoring of factor IX plasma activity should be performed, as well as pharmacokinetic parameters such as recovery and half-life, as clinically indicated, in order to adjust doses as appropriate. The SPC has been updated and states that pharmacokinetics have to be assessed regularly in each patient and posology adjusted accordingly.

Fifty patients completed the study and 7 patients withdrew participation in the study (including one patient who withdrew before treatment). Throughout the study, dosing remained consistent, with 67% of the doses used ranging from >20 to ≤ 50 IU/kg. Analysis of dosing pattern shows that 31 of the 54 evaluable PTPs over an extended length of time required dose adjustment. Of these 31 patients, 16 were less than 15 years of age, an age group in which it has been shown that the average recovery is lower.

Clinical Safety

Information known pre-authorisation

Safety was assessed in both previously treated and untreated patients and reported on the basis of the development of neutralising (inhibitor) and non-neutralising antibodies to FIX. Data were submitted from 44 PTPs, out of whom 39 receiving regularly BeneFIX were monitored up to six months or 50 exposure days.

In addition, the incidence and severity of adverse events, and any changes in the laboratory test results over time, including the results of repeat pharmacokinetic evaluations and seroconversion or evidence of infection to HIV 1 and 2 or hepatitis A, B, or C after repeated exposure to rFIX during the treatment study segments were assessed.

There were 54 adverse events reported that were considered definitely, possibly or probably related to

the study drug by the investigator. The rate of adverse events to number of infusions is 2.2% (54/2418). The rate of adverse events to number of exposure days is 2.3% (54/2333).

- **Viral surveillance** showed no seroconversion to hepatitis A, B, or C with the exception of a patient who received hepatitis A vaccination shortly after enrolling in the study.
- **Thrombogenic potential**
The results of two clinical studies demonstrated that rFIX has extremely low thrombogenic potential.

The occurrence of phlebitis was described in one patient and was rated as possibly related to the use of BeneFIX. One patient experienced a renal infarction: the causality link with the administration of BeneFIX was not established.

The company is asked to carefully monitor for any evidence of thrombogenicity in the BeneFIX treated patients and to submit regularly the relevant data in the Periodic Safety Update Reports. Data on intravascular coagulation markers (Prothrombin fragments 1 and 2, TAT and D-dimer) in at least 12 patients will be submitted in the first periodic safety up-date.

- **Neoantigenicity and Inhibitor development in PTPs**
The current experience with this product, as far as neoantigenicity is concerned, should be considered as limited.

One of the 44 PTPs recruited in the BeneFIX studies has developed a clinically significant persistent inhibitor with a titre of about 1 Bethesda unit. This event was not expected as inhibitor development is an extremely remote event in previously treated Haemophilia B patients. Indeed, the patient had been previously exposed for more than 500 exposure days to pdFIX.

The unexpected development of a persistent inhibitor in one patient treated with BeneFIX could be considered as a signal for a higher neoantigenicity of the rFIX product than plasma derived factor IX.

Therefore, from the presently available data, it cannot be concluded, whether the persistent inhibitor development in one case is an isolated event or whether the rFIX bears the risk of product specific neoantigenicity. The fate and the type of this inhibitor over time will be important observations. Further follow up data on all previously treated patients enrolled in the clinical studies are required by the CPMP. The Company in their response to the CPMP committed to and has completed the PTPs studies (C9407-21 and C9408-21) in which the 44 enrolled patients remained on study for two years. Patients enrolled in the Surgery study (C9417-21) were followed for any adverse events for 12 months.

The potential risk of neoantigenicity and the trend towards the need of increased dosage of BeneFIX should be carefully weighted against inherent risks with pdFIX.

Post-authorisation update

- **Thrombogenic potential**

Data on intravascular coagulation markers were submitted with the first PSUR. Prothrombin fragments 1 and 2, TAT and D-dimer were evaluated for 4 patients. TAT and D-dimer were evaluated for a further 2 patients. There was no evidence of increased coagulation activation, as measured by these coagulation markers, in the 6 patients. Data since 1997 to date (February 2004) indicate that 8 reports of thrombogenicity (plausible diagnosis) have been reported, all associated with indwelling intravenous catheters and/or continuous infusions of BeneFIX.

- **Neoantigenicity and Inhibitor development in PTPs**

The observed alterations in pharmacokinetics as well as the clinical finding of increased factor IX consumption in some patients were signs suggestive of inhibitor formation. Patients have been investigated for inhibitors using 3 assay methods:

- The Bethesda Inhibitor Assay (BIA) with a 5-minute incubation
- The BIA with a 2-hour incubation (the longer incubation increases sensitivity for the detection of hypothetical Type 2 inhibitors.)
- An anti-rFIX ELISA.

The MAH has shown that the ELISA is the most sensitive of the three methods for the detection of both inhibitory and non-inhibitory antibodies to factor IX. The anti-rFIX ELISA and the BIA (5 minute incubation) have been performed on the 52 patients in the study. Samples from 31 patients have been investigated with the BIA (2 hour incubation). To date, one case of low-titre responding transient inhibitor (maximum titre 1.5 BU) has been detected out of 65 BeneFIX patients (including 9 patients participating only in the surgery study). This case was already known.

The MAH is continuing to investigate all patients included in studies for inhibitors. Furthermore, since there have been reports in the literature of a correlation between the occurrence of a factor IX inhibitor to pdFIX and allergic reactions, the MAH will also investigate all patients showing allergic reactions under treatment with BeneFIX for possible inhibitors.

B) Previously Untreated Patients (PUPs)

Study C9418-21 is an ongoing efficacy and safety study of previously untreated patients with severe or moderately severe haemophilia B. Treatment may include primary prophylaxis to prevent all bleeding episodes. According to the protocol the patients in this study will be followed for a minimum of 2 years and up to 100 exposure days or 5 years, whichever is sooner. The PUPs study began in December 1995.

As up to February 1997, 33 PUPs have been enrolled and 19 had received at least one dose of BeneFIX. This is in line with the EU guideline recommendation for pdFIX, which states that at least, fifteen patients should be studied.

Preliminary data indicate that no serious adverse events have occurred, and no inhibitor has been reported. However, in the light that the accrual is still ongoing, and considering that the risk of inhibitors development cannot be ruled out it is recommended that the trial be completed before the indication in PUPs is granted. Indeed, this trial is designed to continue for five years or 100 exposure days per patient, whichever occurs sooner. "Up to now, no conclusive results have been obtained from clinical studies on the treatment of previously untreated patients"-as mentioned in the SPC.

Post-authorisation update

A total of 67 PUPs were enrolled into the study including 4 subjects who were not treated. Out of the 63 treated subjects, 40 completed treatment and final visit as defined by the protocol, 12 withdrew consent or assent, 4 discontinued because of protocol violation or non-compliance, 3 discontinued at the investigator's discretion, 2 discontinued at the sponsor's discretion, 1 discontinued because of FIX inhibitor development, and 1 patient was lost to follow-up.

Two patients out of the 63 patients developed inhibitors after 7 and 15 exposure days. Both were high titre inhibitors. Both patients experienced allergic manifestations in temporal association with their inhibitor development.

C) Post-Authorisation Safety Information

On 31 January 1998 the company has submitted the first periodic safety update report (PSUR) covering the period from 11 February to 11 November 1997. All adverse drug reactions reported by a health care professional from the post marketing experience in the United State during this nine-month period were compiled and analysed. Following the evaluation of this PSUR by the Rapporteur and Co-Rapporteur, concerns were raised about the occurrence of allergic reactions, bleedings and the suspicion of inhibitor development in patients receiving BeneFIX. Information relevant to the latter two issues has been presented in the relevant sections above.

Eleven cases of allergic reactions have been reported. The company has estimated that allergic reactions have been reported in about 2 to 5 patients receiving BeneFIX out of 1000. These reactions could be serious since 3 patients have suffered from anaphylactic reactions considered as life threatening. The non-serious allergic reactions included cutaneous or respiratory symptoms. Three of the patients who experienced allergic reactions had a history of allergy to FIX, including 1 of the 3 patients who suffered from anaphylactic reactions. The aetiology of the remaining cases is still unknown and allergic reactions due to host cell proteins have not been ruled out.

Because of the risk of allergic reactions, patients should be informed of early signs of hypersensitivity reactions, such as hives or shortness of breath, and of the possibility of anaphylactic reaction. The initial administrations of BeneFIX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided. If allergic or anaphylactic-type reactions occur, the administration of BeneFIX has to be discontinued immediately and an appropriate treatment has to be initiated.

It has been reported in the literature that patients developing inhibitors to factor IX may be at an increased risk of anaphylaxis with subsequent challenge with factor IX. Therefore patients experiencing allergic reactions should be evaluated for the presence of an inhibitor although in the patients tested so far there is no proof for additional inhibitor development.

The CPMP considered that further attention should be given to this issue and that the company has to send further information on patients experiencing allergic reactions with the second PSUR. The CPMP considered it appropriate to modify the present SPC and Package Leaflet in order to provide adequate information about this risk to the prescriber and the patient. The amended SPC and Package Leaflet were approved following the submission of a Type II Variation and the Commission Decision was issued on 11 November 1998.

1st Annual Reassessment

The clinical data accumulated at the time of the first and second PSURs confirmed reduced efficacy due to lower recovery compared with pdFIX with a consequent need to increase the dose and/or frequency of dosing. Some allergic reactions, including anaphylaxis, have been reported in the first and second PSURs. Their exact aetiology is still unknown. The MAH has been asked to carefully monitor and investigate patients exhibiting allergic reactions and to continue their investigations into the possibility of inhibitor development. These above mentioned factors have, on an individual basis, to be weighed against the better viral safety profile of rFIX.

The CPMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of the SPC or PL is necessary as part of the Annual Reassessment and that the marketing authorisation remains under exceptional circumstances.

2nd Annual Reassessment

Post licensure experience with rFIX has been obtained from approximately 2885 patients with a total of 254,625,040 IU in the US, Canada and five European countries (Denmark, France, Germany,

Ireland, United Kingdom). In addition 127 patients have been treated or are under treatment in clinical trials.

The recovery of rFIX is lower than the recovery of pdFIX. A need for increased dosing with rFIX can be clearly attributed to the established lower recovery.

Reduced efficacy due to lower recovery compared with pdFIX, i.e. reports of haemorrhage with a consequent need to increase the dose and/or frequency of dosing, is reported in fewer cases during the 4th PSUR observation period. This might be a result of the change of the SPC and Patient Leaflet, adopted by the CPMP on 23 July 1998, addressing this issue.

Allergic reactions, including anaphylaxis, have been reported. Their exact aetiology is still unknown, although the MAH has taken a number of actions to investigate the aetiology of these reactions. The Company has been asked to carefully monitor and investigate patients exhibiting allergic reactions and to continue their investigations into the possibility of inhibitor development.

The progress of these investigations has to be reported with subsequent PSURs. Two phase IV clinical studies evaluating allergic reactions after exposure to BeneFIX are ongoing.

The risk of neoantigenicity was a concern due to the development of an inhibitor in one patient during the PTP study submitted with the original submission. Up to the present time, no further inhibitors have been found in BeneFIX treated PTPs. In addition there has been no evidence of thrombotic events of any clinical significance occurring with BeneFIX treatment during the period covered by the 3rd and 4th PSURs. Furthermore, there is no evidence of transmission of HIV or hepatitis A, B or C as a result of rFIX treatment.

These above mentioned factors have, on an individual basis, to be weighed against the better viral safety profile of rFIX. Therefore a close monitoring for reports of anaphylactic/allergic reactions, inhibitor development, thrombosis and haemorrhage/ lack of effect for BeneFIX must be continued.

No new safety issues have arisen since the first annual reassessment. Most reported adverse events are already included in the SPC and PL or are isolated cases for which there is often a more probable alternative cause other than BeneFIX. No further amendments of the SPC are necessary at the present time.

In view of a favorable safety profile regarding the transmission of infectious agents (BeneFIX does not include as constituents any protein of human or animal origin) a positive benefit/risk profile remains since the first annual re-assessment. However, BeneFIX should be further subject to annual reviews until the open issue of GCP compliance of the PTP as well as the PUP study is solved.

The CPMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of the SPC or PL is necessary as part of this Annual Reassessment and that the marketing authorisation remains under exceptional circumstances.

Conclusion

In view of the limited availability of plasma and the potential risk of transmission of infectious agents by plasma-derived coagulation factor concentrates, there is a public interest in a recombinant blood coagulation factor IX product. The manufacturing process of BeneFIX does not include as constituents any protein of human or animal origin.

Major objections have been addressed by the CPMP on January 21, 1997. The company was able to provide additional clinical data to fulfil requirements of the Note for Guidance (CPMP/BPWP/198/95) regarding the number of followed previously treated patients (PTPs). However, the concern of neoantigenicity raised by the occurrence of an inhibitor in one of the PTPs has not been completely resolved.

The risk of neoantigenicity of this recombinant factor IX was carefully weighed against the risk of contamination with non-enveloped viruses or unknown transmissible agents by pdFIX products, and of shortage of plasma due to plasma batches recall. The need to have a suitable alternative to pdFIX for haemophilia B patients was discussed and acknowledged.

A positive CPMP opinion for granting the marketing authorisation was adopted, under the exceptional circumstances foreseen in Part 4G of the Annex to Council Directive 318/75/EEC, first indent, because “the indication for which the product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence” under normal conditions of use.

The company was asked to carefully monitor PTPs treated with BeneFIX for any evidence of inhibitor occurrence and will submit the relevant data in accordance with the current EU legislation, to follow patients enrolled in the surgery study for any adverse events, to provide additional information on the relation between the dosage and the clinical response in all patients enrolled in the studies, and to carefully monitor the intravascular coagulation markers in the treated patients.

The clinical data accumulated at the time of the first PSUR confirmed reduced efficacy due to lower recovery compared with pdFIX with a consequent need to increase the dose and/or frequency of dosing. Some allergic reactions, including anaphylaxis, have been reported in the first PSUR. Their exact aetiology is still unknown. The company has been asked to carefully monitor and investigate patients exhibiting allergic reactions and to continue their investigations into the possibility of inhibitor development.

Post-marketing experience has produced data in a larger patient population with haemophilia B and has provided additional insight into potential emerging safety issues with the use of BeneFIX. In preparation for post-marketing surveillance, the MAH initially identified 2 areas *a priori* that would require careful monitoring: incidence of inhibitor development and thrombogenicity. After the first year of commercial availability, the MAH identified two additional areas necessitating special vigilance: lack of effect/haemorrhage and allergic-type manifestations.

These above mentioned factors have, on an individual basis, to be weighed against the better viral safety profile of rFIX. Therefore a close monitoring for reports of anaphylactic/allergic reactions, inhibitor development, thrombosis and haemorrhage/ lack of effect for BeneFIX must be continued. The MAH will continue to monitor these issues as part of future PSURs. BeneFIX should be further subject to annual reviews until the open issue of GCP compliance of the PTP as well as the PUP study is solved.