

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of ReFacto. This scientific discussion has been updated until 1 October 2003. For information on changes after this date please refer to module 8B**

### 1. Introduction

ReFacto contains as active substance recombinant coagulation factor VIII (rVIII) (INN= moroctocog alfa) for use in therapy of factor VIII deficiency (Haemophilia A). Moroctocog alfa is a glycoprotein with an approximately molecular mass of 170 kDa consisting of 1438 amino acids. Its amino acid sequence is comparable to the 90 + 80 kDa form of factor VIII (i.e. B-domain deleted), and post-translational modifications that are similar to those of the plasma-derived molecule. Recombinant coagulation factor VIII (rVIII) has functional characteristics comparable to those of endogenous factor VIII.

Factor VIII is the specific clotting factor deficient in patients with haemophilia A. The administration of ReFacto increases functional plasma levels of factor VIII (replacement therapy) and can temporarily correct the coagulation defect in these patients. Activated factor VIII acts as a cofactor for activated factor IX accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed.

A genetically engineered Chinese hamster ovary (CHO) cell line produces ReFacto. The CHO cell line secretes rVIII into a defined cell culture medium that does not contain any proteins derived from human or animal sources (except for pharmaceutical grade human serum albumin), and the protein is purified by a chromatography purification process that yields a high-purity, active product. The potency (IU) is determined using the European Pharmacopoeia chromogenic assay against the WHO standard. The specific activity of ReFacto was 13,000 IU per milligram of protein (it has recently changed to 11,000 IU, see section II, variation II/26). ReFacto is not purified from human blood or plasma and contains no preservatives, added animal and no human proteins in the final formulation.

ReFacto is presented as powder and solvent for solution for injection. The active substance is formulated as a sterile, non-pyrogenic, lyophilised powder preparation for intravenous injection. It is available in single-use vials containing the labelled amount of factor VIII activity, expressed in International Units (IU). Each vial contains nominally 250, 500 or 1.000 IU of rVIII per vial. The formulated product is a clear, colourless solution upon reconstitution and contains sodium chloride, sucrose, L-histidine, calcium chloride, and polysorbate 80.

### Therapeutic practices for Haemophilia A

Haemophilia A is a congenital inherited bleeding disorder caused by a partial or total deficiency of functionally active coagulation factor VIII (anti-haemophilic factor). The bleedings typically begin to occur during early childhood. Although the bleedings can involve any anatomical region they most often involve joints and muscles. Repeated bleedings during childhood may result in destructive changes of the joints with deformity, contractures and muscle atrophy. The degree of factor VIII deficiency correlates with the frequency of clinically significant bleeding. Individuals with the severe form have factor VIII levels < 1% of normal activity (< 0.01-0.02 IU/ml), whereas moderate to mild forms have 1-5% and 5-25% of activity, respectively.

Treatment for haemophilia has for many years been replacement of factor VIII based on infusion of plasma-derived factor VIII concentrates prepared from pooled multi-donor plasma. This has a dramatic effect on the clinical symptoms, given either on demand at episodes of bleedings or prophylactically to protect the patient from spontaneous bleedings. Dosage of factor VIII concentrates is related to the severity of the bleeding and the age of the patient. Recently, factor VIII products prepared by recombinant biotechnology have been introduced, offering the advantage of better viral safety and reducing the demand for blood donor products.

Recent research on the relation between structure and function of the factor VIII molecule has revealed that despite a deletion of the B-domain of the heavy chain of factor VIII, anti-haemophilic activity is

preserved. Thus, rVIII is genetically engineered to consist of an unchanged light chain (80 kDa) in complex with a modified heavy chain (90 kDa), lacking all but 14 amino acids of the large central B-domain.

## **2. Chemical, pharmaceutical and biological aspects**

### **Composition and product development**

ReFacto contains the active substance moroctocog alfa (rVIII), which is a recombinant DNA factor VIII preparation, differing from other factor VIII preparations (recombinant and plasma) in that the B-domain has been deleted. A genetically engineered Chinese hamster ovary (CHO) cell line produces rVIII.

ReFacto is available as a lyophilised powder in three dosage forms: 250 IU, 500 IU and 1000 IU in vials. The powder is reconstituted with isotonic sodium chloride for injection. The powder is provided in 10 ml type I glass vials with stoppers of bromobutyl rubber and the solvent in 8 ml type I glass vials with stoppers of chlorobutyl rubber.

In the clinical trials, three formulations of ReFacto (B, C and D), differing in minor steps of the purification process, have been used. This has been used in combination with minor modifications of the excipient concentrations and with different solvents for reconstitution (sodium chloride and water for injections). Pharmacokinetic comparison has been performed and the use of the different versions is acceptable.

The development pharmaceuticals have been addressed satisfactorily.

The manufacturing process is typical for a protein parenteral product and has been described in sufficient detail. Formulation and filling takes place at Pharmacia & Upjohn, Lindhagensgatan 133, Stockholm, Sweden. Appropriate in-process controls are performed.

The validation of the manufacturing process was performed with three batches of ReFacto, 250 IU and 1000 IU. Detailed and satisfactory experimental data of the validation for ReFacto and the solvent has been provided.

### **Active substance**

Two chains, 90 kDa and 80 kDa, held together by a metal ion bridge, define the B-domain deleted form of factor VIII; both chains are glycosylated. The relative molecular mass is 170 kDa. ReFacto has a total of 1438 amino acids plus 5 % carbohydrate.

### Development genetics

In this section, the assembly of the production strain has been described.

The steps and the assembly of the full length human factor VIII cDNA from a piece of human chromosomal DNA and cDNA sequences from several sources as well as the removal of the major part of the region encoding the B-domain have been sufficiently described.

### Cell Bank System

Data on the preparation and characterisation of the produced master and working cell banks (MCB and WCB) have been provided. The current MCB and WCB specifications, routine stability testing as well as a detailed protocol for the preparation of renewal working cell banks have been provided.

### Fermentation, harvesting and purification

Fermentation, harvesting and primary capture step take place at Pharmacia & Upjohn AB, Strandbergsgatan 47-49 Stockholm and the purification process takes both at Pharmacia & Upjohn AB, Strandbergsgatan 47-49 and Lindhagensgatan 133, Stockholm, Sweden. The fermentation and purification process is adequately controlled, resulting in a consistent product of high purity. Removal of impurities and validation of the production process have been well demonstrated by data on a large number of fermentation and purification runs.

During development, the purification process has been modified to make the process more robust. In total, four purification methods are used (A, B, C and D). Methods C and D were used for the phase II

and III clinical studies. Method D, being the one proposed for marketing, reveals the highest purity and the lowest content of DNA and CHO cell protein. Detailed information on the differences between the purification processes and the batch analysis of the active substance from the different purification schemes have been provided.

The genetic stability data provided proved to be acceptable.

#### Characterisation

The structure of rVIII has been extensively studied by state-of-the-art techniques and was compared to the structure of plasma-derived factor VIII and to the 80 + 90 kDa complex isolated from human plasma. These studies indicate that rVIII and the 80 + 90 kDa form of plasma factor VIII have many common structural characteristics.

#### Physical-chemical characterisation

The full-length FVIII contains 2332 amino acid residues. The A1, A2, and A3 domains have approximately 30% amino acid sequence pair wise homology, and the two C domains 37%. The A and C regions are essential for the function of the molecule. The B domain is not known as having importance for the procoagulation function.

The gene construct of rVIII codes for a single 170 kDa chain which corresponds to the 90 kDa and 80 kDa chains of factor VIII fused by a linker region of 14 amino acids. The primary translation product is produced intracellularly into a heterodimeric 90 kDa + 80 kDa complex held together by a metal ion bridge. The two-chain molecule is secreted into the cell culture medium, together with small amounts of unprocessed primary translation product. In the rVIII molecule, the A1-A2 domains and A3-C1-C2 domains are present. Most of the B domain is deleted except the sequence of 14 amino acids, which joins the A2 and A3 domains.

#### Amino acid sequence

The NH<sub>2</sub>-terminal sequence of the 90 kDa chain and 80 kDa chain has been shown to be consistent with the sequence of plasma derived FVIII.

#### Glycosylation

There are three potential sites in the 90 kDa chain and three in the 80 kDa chain for N-linked glycosylation. Four of these have been found to be glycosylated. In addition, two sites in the 80 kDa chain have been found to be O-glycosylated. The content of sugar is about 5%. The sugar composition and the major part (80%) of the oligosaccharide structures have been determined.

#### Secondary Structure

Far ultraviolet circular dichroism spectroscopy of the plasma factor VIII and rVIII gave similar spectra.

#### Molecular formula

The amino acid composition of rVIII agrees well with the expected sequence and the sequence for plasma derived factor VIII.

Analysis of the primary and secondary structure of rVIII and plasma FVIII produce evidence that the main structural features are the same.

1.  $\leq 10$  % of the 170 kDa single chain in the rVIII.
2. Two forms of 90 kDa chain in rVIII: the 90:1 form with the -COOH terminal end extended with the SQ-link, and the 90:2 form, a truncated form where the SQ link and additional 20 amino acids were missing. The ratio of the two forms varied from 1.0 to 2.1.
3. The COOH-terminal end of 90 kDa chain [90 + 80] kDa form of pdVIII has not been determined due to limited supply of material.
4. Some minor differences in the NH<sub>2</sub>-terminal heterogeneity of the 80 kDa chain.

Original pictures of all the gels have been provided.

### Biological characterisation

The rVIII molecule and the 170 kDa precursor have been compared with plasma factor VIII by activity assays, factor Xa generation, inactivation with activated protein C and in vitro thrombin activation with follow-up of degradation products and binding to von Willebrand factor (vWF). The rVIII and 170 kDa precursor showed little or no difference to plasma factor VIII.

### **Process validation and impurities**

Validation of the production process has been provided and assures consistency of the yield, degree of purity and quality of the active ingredient.

### **Batch analysis**

Results from 25 full-scale batches have been provided.

### **Other ingredients**

All materials used as excipient in the powder for solution for injection (sodium chloride, sucrose, L-histidine, calcium chloride dihydrate and polysorbate 80) and the solvent (sodium chloride and WFI in bulk) comply with Ph.Eur.

### **Control of finished product**

Results from 31 commercial manufacturing batches have been presented to demonstrate consistency of the manufacturing process; analysis of the results shows 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.

Three batches of each strength were stored at 8°C, 25°C, 30°C, 40°C, -20° C for up to 36 months. The methods used to establish the stability of the finish product are: FVIII assay, SEC-HPLC, SD-PAGE, moisture, solubility, appearance, clarity, degree of coloration, particulate matter, sterility, abnormal tox., pyrogens, LAL.

For the finished product a shelf life of 24 months can be accepted. However, real time shelf-life data will be provided on an ongoing basis.

The product may be stored at 25°C for three months within the shelf life. The product must not be returned to the refrigerator.

Viral safety of the product is sufficiently assured by the viral screening of the cell banks, routine testing of the harvest for adventitious viruses and the virus validation studies.

### **GMP**

GMP compliance of the manufacturing process has been assessed by the relevant GMP inspections.

### **Conclusion at the time of authorisation**

The chemical, pharmaceutical and biological part of the dossier concerning ReFacto is carefully documented and overall is satisfactory. As follow-up measures, the company on an ongoing basis will address minor points for clarifications as well as additional information on the manufacturing process. All additional data will be carefully monitored and the results reviewed by the Agency.

## Post-Approval main changes

- **Introduction of an additional strength: ReFacto 2000 IU (Procedure Ref. EMEA/H/C/232/X/22)**

The applicant applied for the 2000 IU dosage strength to ease the use for the number of patients using over 2000 IU per dose.

ReFacto 2000 IU is formulated as a sterile, nonpyrogenic, lyophilised powder preparation for intravenous injection. It is available in single-use vials containing the labelled amount of factor VIII activity, expressed in international units (IU). Each vial contains nominally 2,000 IU of ReFacto per vial. The formulated product is a clear colourless solution upon reconstitution and contains sodium chloride, sucrose, L-histidine, calcium chloride, and Polysorbate 80.

The proposed SPC, labelling and PIL is based on the latest approved product information for the 250 IU, 500 IU and 1000 IU.

A very reduced “Part II” was submitted as the applicant in their approval referred heavily to the original and current application dossier approved for the three other ReFacto dosage strengths, especially regarding the active substance and the virological documentation.

The EU guidelines are fulfilled in general and satisfactory evidence is provided that product manufacture is well controlled, that the consistency of production is achieved and that a satisfactory product results. It is the CPMP opinion that with regards to the chemical/pharmaceutical/biological data no major objections can be raised against a marketing authorisation for ReFacto 2000 IU.

No toxicological evaluation has been performed with Refacto 2000 IU vials. This is considered by the CPMP to be acceptable. No clinical documentation has been submitted with this application. The company satisfactorily justifies for this new strength in the Expert Report.

- **The introduction of a change to Refacto drug product specific activity in the SPC (Ref. Variation II/26)**

A collaborative study conducted by a number of European Official Medicinal Control Laboratories (OMCLs) demonstrated variability among laboratories in the potency assessment of ReFacto using chromogenic substrate assays.

Based on the results of this data, Wyeth applied for a change to the Marketing authorisation to recalibrate the standard used to establish the amount of protein per international unit of the ReFacto drug product. The assigned potency of the current ReFacto reference standard is approximately 20% higher than the value obtained from the recent collaborative study. Using this new potency value, the specific activity is recalculated as 11,000 IU/mg protein instead of the previous 13,000 IU/mg protein. Therefore, based on the favourable assessment of the CPMP and approval of the EC, the Summary of Product Characteristics has been updated to reflect the newly assigned specific activity.

Wyeth intention was to start the introduction of this change in early July 2003, anticipating that that the haemophilia centres as well as hospital pharmacies in connection with haemophilia centres would switch their existing ReFacto inventory to new ReFacto by September 2003.

(For more information, please see module “steps taken after” & and EMEA Public Statement on ReFacto dated 27.05.03).

## Conclusion

To date the chemical, pharmaceutical and biological part of the dossier concerning ReFacto remains carefully documented and overall is satisfactory.

### **3. Toxicopharmacological aspects**

The safety assessment of sucrose and polysorbate 80 and chemical substances (ethylene glycol, tributyl phosphate, and Triton X-100) used in the production of rVIII has been provided. These substances raise no safety concerns. It is considered that a sufficient safety margin exists at the proposed specified residue limits.

#### Characterisation of the rVIII molecular complex

rVIII is a deletion version of human coagulation factor VIII. The molecule has been genetically engineered to correspond to the smallest of the multiple active forms of factor VIII found in plasma-derived factor VIII concentrates. A genetically engineered Chinese hamster ovary (CHO) cell line produces rVIII.

The rationale for drug design was that the B-domain was most likely not required for expression of biological activity. The overall size of the full-length molecule has been decreased by approximately 40% from 2332 to 1438 amino acids, by replacing the B-domain of 908 amino acids with a short peptide linker of 14 amino acids, derived from the ends of the B-domain. rVIII molecule is composed of two polypeptide chains, 90 and 80 kDa, held together by a metal ion bridge.

Thus, rVIII is similar but not completely identical to the 90 + 80 kDa complex isolated from human blood.

Overall, rVIII behaves qualitatively and quantitatively as pVIII.

#### **Batches used in the preclinical programme**

Batches from purification methods A through D were used as test material during preclinical development. These methodology improvements involved improvements of purification without changes in rVIII structure or functional activity.

#### **Pharmacodynamics**

##### **Primary pharmacodynamics**

Despite observed differences in the clearance and in the volume of distribution at steady state between rVIII and the comparator plasma-derived factor VIII, Octonativ-M in haemophilic dogs, both preparations were similarly effective and showed a similar plasma half-life. The doses employed (125 and 500 IU/kg) were 4- to 16-fold higher than the intended therapeutic dose. The animal data are considered sufficient in view of the clinical documentation.

The in vitro and in vivo (haemophilia A dogs model) pharmacodynamic studies presented an improved haemostasis as well as restoring of the clotting defect were shown support the proposed use in man. From the studies, it is concluded that the biological functionality of the rVIII molecule is essentially similar to that of plasma derived factor VIII, including binding properties to vWF.

#### **Safety pharmacology**

A relevant safety pharmacology study was performed, examining the cardiovascular and respiratory systems in dogs. No safety issues were detected.

#### **Pharmacokinetics**

No studies were performed to address distribution, biodegradation or excretion. However, such information is not required for this particular product.

The intravenous pharmacokinetics of rVIII were examined in the haemophilia A dog and the Cynomolgus monkey. Overall, the pharmacokinetic profile of rVIII in haemophilia A dogs was comparable to that of plasma-derived factor VIII. In the Cynomolgus monkey the pharmacokinetic profile of rVIII was almost similar to full length non-proteolytically processed 170 kD protein.

Clinically, based on the above-referenced animal data, it should be expected that rVIII has a similar kinetic profile to that plasma-derived factor VIII.

No kinetic data of rVIII in rats have been submitted, which is considered acceptable in light of the exaggerated systemic exposure demonstrated in the dog and monkey.

## **Toxicology**

### **Single dose toxicity**

Single i.v. dose toxicity was studied in rats and cynomolgus monkeys. No treatment-related findings occurred.

### **Repeated dose toxicity**

Repeated i.v. dose toxicity was studied in rats (up to 28-30 days) and in cynomolgus monkeys (up to 13 weeks). rVIII was immunogenic in both species. In rats, no treatment-related toxicity occurred. In cynomolgus monkeys, haemorrhagic lesions were induced (predominantly in the heart) probably due to the neutralising antibody response to both administered recombinant human and endogenous monkey factor VIII. Similar findings were noted in cynomolgus monkeys treated with plasma-derived factor VIII (Octonativ-M).

### **Reproduction studies**

No reproductive toxicity studies were conducted. This poses no problem for this particular product.

### Mutagenic potential

An in vivo micronucleus assay in mice was negative. Further testing is not needed.

### Oncogenic/carcinogenic potential

No carcinogenicity studies were performed. These are not needed in view of the nature of the product and its proposed indication.

### Local tolerance

In beagles, single paravenous and intra-arterial administration was well tolerated.

### **Special toxicity studies**

Two immunogenicity studies were conducted in cynomolgus monkeys. The first one compared i.v. and s.c. administration of rVIII during 6 weeks and revealed a somewhat different anti-rVIII antibody response. The second one compared rVIII and Octonativ-M given by repeated i.v. dosing over a period of 13 weeks. No obvious difference was noted.

### **GLP**

All pivotal safety studies were conducted in compliance with GLP regulations.

### **Conclusion on preclinical pharmacology and toxicology**

The preclinical programme of rVIII is of high quality and adequately designed in respect to the recombinant DNA-technology based/human protein nature of the rVIII molecule. Key safety studies were performed according to GLPs.

## **4. Clinical aspects**

### **Pharmacodynamics**

No specific pharmacodynamic studies have been carried out. Considering the replacement therapy of coagulation factor VIII, which is an endogenous clotting factor in human plasma, these studies are not mandatory.

## Pharmacokinetics

As previously mentioned in this assessment, several formulations of rVIII have been prepared during the development process of the product. Formulation “D” is the product which intended for marketing.

Eighteen patients with severe haemophilia A were included in a pivotal randomised, multicentre, three-way cross over study (Report 97 10 751) comparing pharmacokinetic data after single dose infusion of rVIII of formulation “C” and formulation “D” with a commercially available plasma-derived factor VIII concentrate (Hemofil®-M). All patients had at least one year of earlier treatment with factor VIII concentrate. The single injections were separated by a wash-out period of at least five days. The dose given was 50 IU/kg.

It was possible to show bioequivalence between formulations “C” and “D” for all parameters. The AUC of rVIII was slightly higher than that of Hemofil®-M, but the difference was not statistically significant and the ratio of 1.13-1.15 is within the accepted variation of 80-120%.

Conclusion: ReFacto has pharmacokinetic properties similar to a plasma-derived factor VIII product with respect to all important parameters, which makes clinical efficacy highly likely.

Repeated pharmacokinetic analysis after 12 months in a large number of patients found unchanged results for recovery and elimination half-life.

## Clinical experience

All efficacy and safety aspects meet the requirements of the guideline for assessment of efficacy and safety of plasma derived factor VIII products (CPMP/BPWP/198/95), except for viral safety. However, these guidelines can only be taken as a recommendation, especially because they are not intended to cover the development of recombinant DNA coagulation factors.

Owing to the fact that rVIII is a high-purity product and the CHO cell line secretes rVIII into a defined cell culture medium free of proteins derived from animal sources, the assessment of viral safety in clinical studies (e.g. previously untreated patients) is not mandatory.

The major safety issue is the development of neutralising antibodies (inhibitors) due to the immunogenicity of factor VIII molecules infused into a patient with no or very low levels of endogenous factor VIII. Inhibitors partly or completely abolish the effect of replacement therapy. The neoantigenicity of a new brand of factor VIII is best assessed in previously treated patients (SSC recommendation of ISTH, White et al., Thrombosis and Haemostasis in Press 1999). The magnitude of the inhibitor in a patient is expressed in Bethesda Units/ml (BU/ml). One BU/ml inhibits 50% (0.5 IU) of factor VIII activity in 1 ml of normal plasma.

Clinical efficacy of a factor VIII product includes studies of previously treated patients (PTP) as well as previously untreated patients (PUP). The efficacy during surgical procedures was also evaluated.

### PTP-studies (No. 97 10 778)

One hundred and six patients of 108 completed the study according to the protocol. All patients had previously been treated with blood formulations between 5 and 49 years before this study. All patients had to have severe haemophilia A (factor VIII < 2%). The age of the 108 patients was between 8 and 73 years (median 26 years and mean 28 years). Twenty-nine patients were HIV positive. HIV status was unknown for two patients at study start. Ninety-six patients were positive for hepatitis C. Hepatitis C status was unknown for two patients at study start. All but one of the HIV positive patients were also positive for hepatitis C. Seventy patients were positive for hepatitis B antibody. The 108 patients received a total of 10,887 rVIII injections, ranging from 1 to 647 injections per patient for a cumulative total of 21,325,930 IU rVIII infused. The total number of exposure days was 10,023 ranging from 1 to 348 exposure days per patient with a median of 78 days (mean 93 days). One hundred and five patients were treated on demand for bleeding episodes and 89 patients received prophylactic treatment. Bleeding episodes were treated with an average dose of 29 IU/kg rVIII per injection and prophylactic treatment averaged 26 IU/kg rVIII per injection.

The number of patients with severe haemophilia A has been considered sufficient. Unfortunately, most patients were positive for hepatitis C and some for HIV. Although HIV status is likely to affect the immune status of the patient, this is not a major problem, as the previously untreated population (to be discussed below) is the population mostly at risk for inhibitors after exposure to FVIII products.



### **PUP studies (97 10 641)**

Eighty-seven patients were included with a mean age of 10 months (range 0-52 months) at inclusion. The studies were conducted in 46 centres in 15 countries. Patients had to have severe haemophilia A (factor VIII: C < 0.02 IU/ml). The study drug was given in two forms, "C" formulation was given at the beginning of the study and "D" formulation at a later stage. As previously discussed, the two rVIII formulations are biopharmaceutically equivalent. The mean dose used for bleeding episodes was 53 IU/kg (range 26 to 156 IU/kg). The investigator, for each injection given for a bleeding episode, assessed the haemostatic effect. The investigator conducted a global efficacy assessment using a 5-graded subjective scale every three months.

### **Surgery studies (97 10781):**

Twenty-five male patients with moderate (factor VIII 2-5%) or severe (factor VIII < 2%) haemophilia A were treated with rVIII before and after surgical procedures. The type of surgical procedures in previously treated and untreated patients show that most previously treated patients underwent procedures related to the joints, such as total knee replacement. PUPs surgical procedures consisted primarily of Port-A-Cath insertion. A mean pre-surgery dose of 59 IU/kg in the PTPs produced a factor VIII level close to the normal level (0.966 IU/ml).

### **Therapeutic efficacy**

#### **PTP-studies (No. 97 10 778)**

One hundred and five patients reported 2380 bleeding episodes during the study. Seventy-one percent of all bleeding episodes required only one single injection of rVIII for resolution. Ninety-three percent of the bleedings were resolved after one, two or three injections. The majority of bleeding episodes were categorised as joint bleeds (n=1867), 449 were muscle, soft tissue and unspecified bleeds and 64 affected other specified tissues. The assessment was made by either the patient (when the treatment was administered at home) or by the investigator (when the injection of rVIII was administered in hospital). Assessment revealed that out of 561 global assessments on a 5-graded scale, 554 (99%) were rated as "very useful" or "useful". Six of the remaining assessments were "slightly useful" and one rating was "useless". At the start of the study (n=87) and after 12 months the mean in vivo recovery was 132% and 132% and the mean elimination half-life 10.4 and 10.5 hours respectively. The data shows that recovery (%) and elimination half-life (h) does not change over time.

It is concluded that efficacy has been adequately shown by the results of the investigators' and patients' rating of efficacy in 105 patients reporting 2380 bleeding episodes.

### **PUP studies (97 10 641)**

Sixty-four percent (276 of 429) bleeding episodes were resolved with a single infusion. Ninety-one percent (389/429) of bleeding episodes were resolved within three infusions. The investigator rated response for each injection given for a bleeding episode. Haemostatic effect was rated "excellent" or "good" of 92.5% of injections (all bleeds), 87% for joint, 94.5% for muscle/soft tissue and 98% for other specified tissues. Prophylactic treatment was given to four patients who received a total of 174 injections over a mean duration of 17 weeks (mean dose of 41 IU/kg per injection). There were no break-through bleeding episodes.

### **Surgery studies (97 10781)**

A factor VIII level close to normal was maintained during the rest of the day of surgery. This required a mean maintenance dosage of 85 IU/kg. During the week following surgery a mean dosage of 565 IU/kg/week was given. The haemostasis was judged as "excellent or good" after all 28 surgical procedures. The blood loss during the day of surgery was judged as normal for the 26 procedures where assessments were made. Transfusions were required in only two out of the 28 procedures. One comment that can be made is the large amount of factor VIII used in the surgical replacement therapy.

However, the fact that in most patients the dose of substitution during the first week is low or normal in comparison with literature data regarding the first post-operative week is reassuring. rFVIII-SQ has been tested in sufficient surgical procedures (28) and effective haemostasis was achieved and maintained in 28 surgical procedures.

## Safety

The main efficacy data come from the cumulative safety data from studies in PTPs, PUPs and patients undergoing surgery. First, a summary of the results of the initial safety studies (95 10 592, 96 10 593 and 96 10 546) conducted in a small number of patients is provided.

### Safety study 95 10 592

Six patients with severe haemophilia (factor VIII: C  $\leq$  0.01 IU/ml) were included in an open, non-comparative, three-centre study. The results showed that rVIII was well tolerated. There were no adverse reactions and no FVIII inhibitors were found. No antibodies to FVIII, CHO cell-derived components or mouse IgG were found. The investigator rated the treatment as "very useful" or "useful" in all 6 cases.

### Safety study 96 10 593

Three previously treated patients received prophylactic rVIII three times weekly during four weeks. The C-formulation was used. One case of mild rise in body temperature was observed after the first injection only. No inhibitors were found. The treatment was evaluated as "useful".

### Safety study 96 10 546

Four previously treated patients received prophylactic rVIII three times per week during four weeks. The C-formulation was used. The rVIII was well tolerated and no inhibitors were found. There were no increases in antibodies to CHO-derived components or mouse IgG. The treatment was evaluated as "very useful" and "useful" by the investigator as well as by the patient.

### Cumulative safety data from studies (PTPs, PUPs and patients undergoing surgery)

The applicant provides an updated report summarising all cumulative safety data from the three studies (PTPs, PUPs and patients undergoing surgery). The data lock-point for the safety study, at the time of the submission of the dossier, was May 1997. The safety of rVIII has been assessed in a total of 213 patients (97 PUPs, 112 PTPs and 4 patients undergoing surgery only). It should be noted that 33 of the patients who underwent surgical intervention were recruited from one of the other studies. Patients in the pivotal studies had received at least one injection of rVIII. Thirty-eight batches of rVIII were used, 20 of C formulation and 18 of D formulation. Three patients died during the studies. Two (2) were diagnosed as HIV positive and Hepatitis C positive prior to enrolment in the trial. The third patient had severe haemophilia A and developed high titre inhibitors not neutralized when treated with immune tolerance therapy. These deaths were considered not related to rVIII treatment.

In addition to inhibitor reports in 26 patients, 72 adverse events which were rated as probably or possibly related to therapy were reported. Fifteen patients experienced 21 serious adverse events where the causal relationship to rVIII was rated as possible or probable by the investigator and are therefore classified as adverse reactions. Eleven of these serious adverse drug reactions were associated with inhibitor formation (see below). The remaining 10 serious adverse drug reactions in 6 patients were increased AST, and ALT, infected haematoma, pain in little finger, weakness in adduction and abduction, fever, removal of Port-a-Cath, Port-a-Cath implantation and anaphylactic reaction. Allergic type reactions (including anaphylactic-type reactions) are described in the SPC.

Seven (out of 100) patients were withdrawn from the PUP study and ten (out of 114) from the PTP study. In five patients (3 in PTPs and 2 in PUPs) there were clinically significant changes in clinical chemistry or haematology tests. All these tests were aberrations in liver function tests and in one case a slight increase in CK-MB.

### Inhibitors

At the cut-off date of October 1996, when 87 patients had at least once required therapy with rVIII, 17 patients (19%) had developed inhibitors to factor VIII after a median exposure of 11 days (table 2). Seven were high responders (BU/ml  $\geq$  5) and 10 were low responders with a peak level of  $<$  5 BU. In 3 patients the detectable inhibitor titre was present on a single occasion only. The mean age at inclusion in the study was 10.5 months (median 9 months). The mean interval between the first injections and inhibitor detection was 6 months. The median number of exposure days at inhibitor detection was 11 days (mean 12.5 days, range 4-50 days). A Kaplan-Meier analysis showed that inhibitor development occurred at a risk of 25% after 13 exposure days. The inhibitor disappeared spontaneously in 4 patients

and in another four during immune tolerance treatment. The assessment of the response to the rVIII treatment in inhibitor patients is indicated in table 1. In the safety summary report 97 107 90 all cumulative data from the PUP and PTP studies and patients were summarized (cut-off point 31 May 1997). At that time a total of twenty-six patients out of 97 PUPs (27%) developed inhibitors. Nine of the PUPs with inhibitors were high responders ( $\geq 5$  BU/ml), and six of these had peak values  $\geq 10$  BU/ml.

**Table 1: Assessment of the response to the r-VIII treatment in inhibitor patients (PUP study No. 97 10 641)**

Assessment	All bleeds		Joint bleeds		Muscle, soft tissue and unspecified		Other specified tissues	
	Number	%	Number	%	Number	%	Number	%
excellent	66	45	27	46	23	46	16	43
Good	50	34	23	39	15	30	12	32
Fair	30	21	9	15	12	24	9	24
None	0	0	0	0	0	0	0	0
Total	146	100	59	100	50	100	37	100

An increase in the incidence of inhibitors from the report of November 1996 (19%) to May 1997 (27%) of previously untreated patients was observed (table 2). The applicant submitted updated documentation for inhibitor development. Data available from January 1998 concerns 101 patients with a median exposure of 20 days and an inhibitor incidence of 29% (29 patients of 101 patients). Five patients with low-titre inhibitor have, after re-evaluation, been considered false positive reactions due to methodological aspects of the assay.

An important observation is that the median number of exposure days until inhibitor development has remained constant (12 days) while the median number of exposure days has increased from 9 to 20 days. Moreover, so far no patient has been observed developing an inhibitor after 50 days of exposure. In a Kaplan-Meier estimate, this translates into a plateau after 18 exposure days and, on extended observation, the probability of remaining inhibitor-free continues at 70%. These observations are very similar to other licensed recombinant factor VIII products.

In addition, both formulations "C" and "D" have been used in the PUP-study and it can not be totally excluded that these formulations have different immunogenicity characteristics. In 2 (out of 112) PTPs (2%) inhibitors to factor VIII were suspected based on local tests but could not be confirmed in the Bethesda Inhibitor Assay at the central laboratory.

Laboratory significant increases of antibodies to CHO-cell derived components were reported in 14 PTPs and 12 PUPs. Significant increases of antibodies to mouse IgG were also reported in 3 PTPs and 8 PUPs. The rise was only transient in some patients. No clinical symptoms were associated with the rise in any of the patients and in no case did it prevent further treatment with rVIII.

**Table 2: Inhibitor data in previously untreated patients**

	1 November 1996	31 May 1997	31 January 1998
Incidence of inhibitor	17/87 (19%)	26/ 97 (27%)	29/101 (29%)
-high responder (peak level $\geq 5$ BU/ml)	7	9 (6 $\geq 10$ BU)	15 (10 $\geq 10$ BU)
-low responder (peak level $< 5$ BU/ml)	10	17	14
Median number of exposure days at inhibitor detection	11	12	12

In summary, ReFacto treatment is associated with an incidence of inhibitor induction in previously untreated patients of approximately 20 – 30%, which is similar to the results of other factor VIII products as reported in the literature. The company is committed to improve the statistical evaluation of the inhibitor incidence to give a more precise picture in the on-going PUP study.

Post-approval submitted clinical data: Additional Phase III clinical data on Inhibitors

Following the 2<sup>nd</sup> PSUR (Periodic Safety Update Report 31.01.98 – 31.08.99), data from ongoing trials have revealed that 32% of PUPs treated with ReFacto developed inhibitors: 16% with a titre  $\geq$  5 BU and 16% with a titre below 5 BU. Interim data from these studies were initially submitted at the time of the MAA submission. The median number of exposure days up to inhibitor development in these patients was 12 days (range 3-49 days). One of 113 (0.9%) PTPs developed an inhibitor. Inhibitor development occurred in the same time frame as the development of monoclonal gammopathy of uncertain significance. The development of inhibitor was associated with a bleeding episode that failed to respond to ReFacto treatment. Eighteen of 113 (16%) PTPs had an increase in anti-CHO antibody titre, without any apparent clinical effect. The anti-CHO antibody titres decreased to below threshold levels at subsequent assessment time-points in 14/18 patients (78%).

The SPC has been updated in line with recommended core SPC for factor VIII and IX products, resulting in a number of changes. These include: i) replacement of the dosing table for patients with bleeding episodes and/or surgery, ii) information on the differences in dose and frequency of administration for children including new-borns, iii) pharmacodynamic data in children < 6 yrs old, iv) general information on the formation of neutralising antibodies (inhibitors), v) statements on lack of effect, mainly in prophylaxis patients and a recommendation to consider alternative therapies in patients with high inhibitor titres, where Factor VIII therapy may not be effective and vi) a recommendation to register the patient's name and product batch number after each administration has been inserted.

#### **Overall benefit/risk analysis**

Based on the assessment of the quality, safety, and efficacy documentation of ReFacto (rVIII), and with due consideration to the CPMP Note for Guidance to Assess Efficacy and Safety of Human Plasma derived Factor VIII:C and Factor IX:C Products in Clinical Trials in Haemophiliacs before and after Authorisation (CPMP adopted Feb.96) (CPMP/BPMP/198/95), the benefit/risk ratio for ReFacto is positive. Therefore, a marketing authorisation is recommended.

#### **5. Overall conclusions**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP, 17 December 1998, considered by consensus that the benefit/risk profile of ReFacto was favourable in the treatment of hemophilia A (congenital factor VIII deficiency or classic hemophilia) and prevention of bleeding (prophylaxis).

As with other factor VIII products, it has been recommended to give the legal status of a medicinal product subject to restricted medical prescription.

To date the chemical, pharmaceutical and biological part of the dossier concerning ReFacto remains carefully documented and overall is satisfactory. The final data on quality, safety and efficacy which were provided after the CPMP opinion was granted did not affect the benefit/risk ratio of ReFacto but led to adequate changes to the product information.