ASSESSING THE EFFICACY AND SAFETY OF HUMAN PLASMA DERIVED FACTOR VIII:c AND FACTOR IX:c PRODUCTS IN CLINICAL TRIALS IN HAEMOPHILIACS BEFORE AND AFTER AUTHORISATION

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Additional Notes  This note for guidance describes the clinical trials required for authorisation with respect to two different human plasma derived factor VIII and Factor IX products: 1) Products for which a marketing authorisation is to be submitted and 2) Authorised products in which a change in the manufacturing process has been made.

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ASSESSING THE EFFICACY AND SAFETY OF HUMAN PLASMA DERIVED FACTOR VIII:C AND FACTOR IX:C PRODUCTS IN CLINICAL TRIALS IN HAEMOPHILIACS BEFORE AND AFTER AUTHORISATION

1. INTRODUCTION

Before, 1960, plasma was the only agent generally available for the treatment of the hereditary coagulation disorders. Several plasma product concentrates are now available for this purpose which have been purified and virally inactivated in various ways. With respect to factor VIII deficiency the replacement therapy consists of factor VIII concentrates of different purity. Random reports of a relatively high incidence of inhibitors after administration of factor VIII products together with reports of viral infections (hepatitis C, hepatitis A and HIV) after administration of human plasma derived coagulation factors, has made the regulatory authorities more aware of the potential risks of these products. As one of several measures aimed at improving viral safety of blood products, it is necessary to demand adequate clinical investigation before a marketing approval is granted. Clinical trials are necessary addressing efficacy, safety with respect to transmission of viral infections and immunogenicity for FVIII and FIX concentrates. In addition in applications for FIX concentrates thrombogenicity should be addressed.

In view of outbreaks of hepatitis A among haemophiliacs treated with a solvent detergent factor VIII in 1992 the Committee on Proprietary Medicinal Products (CPMP) approved the position paper of the biotechnology working party (III/5830/93 Final) on blood products and non-enveloped viruses. It was recommended that the manufacturing process should include viral inactivation/removal which is also effective against non-enveloped virus. As a virus inactivation/removal step (or any change in the purification process) may alter the structure of the coagulation factor and/or induce loss of activity, efficacy and immunogenicity data are clearly needed. This guideline describes the clinical trials required for authorisation with respect to two different human plasma derived factor VIII and Factor IX products:

1) Products for which a marketing authorisation is to be submitted.

2) Authorised products in which a change in the manufacturing process has been made (e.g. additional viral inactivation step).

The clinical trials should be performed according to the guidelines on Good Clinical Practice.

Recombinant DNA products are excluded from this guideline.
2. PRODUCTS FOR WHICH A MARKETING AUTHORISATION IS APPLIED

2.1 Efficacy
In clinically evaluating a new human plasma derived coagulation factor for the treatment of haemophilia A or B patients, the initial trial is typically one that examines the pharmacokinetics of the principal active factor. Half life and recovery data are the most important (surrogate) endpoints for efficacy of a new factor VIII or Factor IX product. The guideline below is according to the guidelines proposed by the International Society of Thrombosis and Haemostasis (ISTH) (Thrombosis and Haemostasis 1991; 66 (3):384-386).

2.2 Safety
Safety aspects of a new factor VIII or Factor IX product refer to viral safety, immunogenicity and any other adverse events. For factor IX products thrombogenicity should also be considered as a safety issue.

2.2.1 Adverse events
All adverse events after infusion of the new product should be reported.

2.2.2 Viral Safety
Manufacturers of coagulation factor concentrates are obliged to optimise viral safety by rigorous selection of donors, screening of donations, including testing for HBsAg, antibody to hepatitis C virus, antibody to HIV 1+2 and by using appropriate viral elimination/inactivation methods according to the requirements in CPMP guideline Medicinal Products derived from Human Blood and Plasma and Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses. Three principal complementary approaches are adopted to control potential viral contamination of coagulation factor products: selecting and testing source material, testing the capacity of the production process to remove or inactivate viruses, and testing the product at appropriate stages of production for absence from contaminating viruses.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of ineffective agents cannot be totally excluded. This applies also to hitherto unknown pathogens. The current procedures applied in the manufacture of medicinal products derived from human blood or plasma are effective against enveloped viruses such as HIV and Hepatitis B and C. These procedures are of limited value against non-enveloped viruses such as Hepatitis A and Parvovirus B19.

All patients included in the trials should be followed up for safety issues according to a protocol described in the appendix.

2.2.3 Immunogenicity
2.2.3.1 Factor VIII products
The occurrence of antibodies against factor VIII is one of the major possible complications of haemophilia treatment. The risk of inhibitor occurrence is higher in patients with severe
haemophilia A than in patients with moderate and mild disease. Inhibitor risk may be associated with commencing or changing treatment or where the antigenicity of the product has been altered due to changes in the manufacturing process. Prior to authorisation immunogenicity of a new factor VIII product should be investigated first in previously treated patients (PTPs) and then, depending on the claimed indication, in previously untreated patients (PUPs). The Summary of Product Characteristics (SPC) should include a section stating the experience with respect to immunogenicity in PUPs or state that there is no such experience.

2.2.3.2 Factor IX products

Haemophilia B is from 4 to 8 times less common than haemophilia A. The incidence of inhibitors in these patients after administration of factor IX is rarer than in Haemophilia A patients. Inhibitors to factor IX have been demonstrated in approximately 4% of patients with severe haemophilia B. Nevertheless with the development of purified factor IX concentrates the immunogenicity should be investigated prior to authorisation of factor IX products. The SPC should include a section stating the experience with respect to immunogenicity in PUPs or state that there is no such experience.

2.2.4 Thrombogenicity (factor IX products)

Treatment with Factor IX concentrates containing Factors II, VII and X has been associated with a risk of thrombosis. Purified Factor IX products have been shown to be associated with a lower thrombogenic risk. For all new factor IX concentrates testing for markers of activation of coagulation should be carried out in the non-bleeding state.

2.3 Clinical trials with factor VIII products

2.3.1 Pre-Authorisation

2.3.1.1 Efficacy

A pharmacokinetic trial, measuring half-life and recovery, should be performed in at least 12 subjects with haemophilia A (factor VIII < 2%) without inhibitor and not actively bleeding. Patients should be at least 12 years of age and should not have received an infusion of concentrate in at least the past 3 days (if possible 7 days). Samples for factor VIII activity determination should be taken before injection of 25-50 IU/kg of the new factor VIII product and between 15 and 30 minutes, 1, 3, 6, 9, 12, 24 and 30-36 hours after the infusion. At least 3 different lots should be employed in the trial. Recovery should be determined from the peak factor VIII activity in the first four sample time periods post-infusion.

Patients who participated in the pharmacokinetic trial should continue treatment with the product for 6 months and at least 5 patients should be tested for half-life and recovery after 3-6 months.

Clinical efficacy and tolerability after administration should be assessed from the clinical response as reported by patients in the safety trials (see 2.3.2) at the regular visits. Response should be assessed as “none”, “moderate”, “good” or “excellent” by the physician for those patients who were treated with the product for major bleeds. In addition, response will be determined by the physician in a minimum of 5 patients undergoing at least 10 surgical procedures, including achievement of haemostasis, loss of blood and requirement for transfusion.
23.1.2 Safety

Clinical safety will be assessed in all patients receiving the new factor VIII product.

- In hospitalised patients, such as patients included in the pharmacokinetic trial, for blood pressure, heart rate, temperature, respiratory rate and adverse events.

- In out-patients for adverse events.

2.3.1.2.1 PTP (Previously treated patient) study

A minimum of 30 immunocompetent (CD4 lymphocytes > 400/ml) previously treated patients with severe haemophilia A with at least 10 exposure days to the new factor VIII product and a follow up of at least 6 months for all patients must be included prospectively.

Immunogenicity

The factor VIII inhibitor titre will be determined every 3 months. An interim analysis will be performed when 30 patients not having undergone surgery have been treated for 6 months with a minimum of 10 exposure days each. The titre of the inhibitor should be reported in Bethesda Units (BU) as well as the clinical relevance, the cumulative incidence and the number of exposure days (also in relation to development of inhibitors).

Viral safety

According to EC Good Clinical Practice the PTP patients should be followed up for viral safety markers. Full baseline data for markers of viral infection (aminotransferase, HIV 1+2 ab, HCV ab, HBV antigen and ab and HAV ab) should be provided according to the table in Appendix 1. All patients negative for these markers should have regular testing according to the schedule in the Table. In patients who are Parvovirus B19 antibody negative at entry a sample should be tested using gene amplification methods at one week after the first treatment. Serum samples should be stored at -70°C whenever the patient is sampled, for possible future testing. No claims can be made in the SPC on viral safety of the product with respect to parvovirus B19 transmission.

2.3.1.2.2 PUP (previously untreated patient) study

PUP studies should be carried out, or at least initiated. The SPC should include a section stating the experience with respect to inhibitor development in PUPs or state that there is no such experience. A PUP study should be done only after results of the PTP trial are available and according to the guideline.

An open label uncontrolled multicentre trial in previously untreated severe haemophilia A patients should include at least 20 patients. These patients should be tested for viral safety and inhibitor development.

Viral safety

Viral safety data (serum aminotransferases, HIV, hepatitis C) should be monitored at 3 month intervals for at least 2 years and be reported at 6 month intervals. In patients who are Parvovirus B19 antibody negative at entry a sample should be tested using gene amplification methods at one week after the first treatment. Serum samples should be stored at -70°C whenever the patient is sampled, for possible future testing.

Immunogenicity

The patients should be tested every 3 months for at least 100 exposure days or 5 years whichever comes first. The titre of the inhibitors should be reported (Bethesda Units = BU) as well as the clinical relevance, the cumulative incidence and the number of exposure days.
2.3.2 Post-Authorisation

2.3.2.1 PTP

After authorisation laboratory parameters (according to the table in the appendix) from at least 50 PTPs treated for at least 2 years should be included in the Periodic Safety Update.

2.3.2.2 PUP

Immunogenicity and viral safety data (including parvovirus B19 seroconversion) on any PUPs treated with the product should be included in the Periodic Safety Update as described in the note for guidance Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Medicinal Products.

2.4 Clinical trials with factor IX products

2.4.1 Pre-Authorisation

2.4.1.1 Efficacy

A pharmacokinetic trial, measuring half-life and recovery, should be performed in at least 10 subjects with haemophilia B (factor IX ≤2%). Patients should be at least 12 years of age and should not have received an infusion of concentrate in at least the past 4 days (if possible 7 days). Samples for factor IX activity determination should be taken before injection of 50-75 IU/kg of the new factor IX product and 30 minutes, 1, 3, 6, 9, 12, 24, 30, 36 and 50 hours after the infusion. At least 3 different lots should be employed in the trial. Recovery should be determined from the peak factor IX activity in the first four sample time periods post-infusion.

Patients who participated in the pharmacokinetic trial should continue treatment with the product for 6 months and at least 5 patients should be tested again for half life and recovery after 3-6 months.

Clinical efficacy and tolerability after administration should be assessed from the clinical response as reported by patients in the safety trials (see 2.4.2) at the regular visits. Response should be assessed as “none”, “moderate”, “good” or “excellent” by the physician for those patients who were treated with the product for major bleeds. In addition, response will be determined by the physician in a minimum of 5 patients undergoing at least 10 surgical procedures, including achievement of haemostasis, loss of blood and requirement of transfusions.

2.4.1.2 Safety

In addition to the requirements for factor VIII products, tests for activation of coagulation after administration of the product should be carried out. This should be determined in the patients of the pharmacokinetic trial as well in a minimum of 5 patients undergoing at least 10 surgical procedures. In the surgical patients clinical evaluation of thrombosis should be undertaken by safe, objective means. Due to the lower incidence of haemophilia B as compared to haemophilia A, the number of previously treated patients followed up for viral safety and immunogenicity should be lower than for factor VIII products: 12 for viral safety and 20 patients for immunogenicity. If a PUP study is done, it should include 15 patients.
2.4.2 Post-Authorisation

2.4.2.1 PTP

After authorisation, laboratory parameters (according to the table in the appendix in the appendix) from at least 30 PTPs treated for at least 2 years should be included in the Periodic Safety Update.

2.4.2.2 PUP

Immunogenicity and viral safety data (including parvovirus B19 seroconversion) on any PUPs treated with the produce should be included in the Periodic Safety Update.

3. AUTHORISED PRODUCTS IN WHICH A CHANGE IN THE MANUFACTURING PROCESS HAS BEEN MADE (E.G. ADDITIONAL VIRAL INACTIVATION STEP)

3.1 Efficacy

As a virus inactivation/removal step (or any change in the purification process) may alter the structure of the coagulation factor and/or induce loss of activity, pharmacokinetic studies, measuring half-life and recovery are clearly needed.

3.2 Safety

Viral safety

If the additional viral reduction process concerns reduction of non-enveloped viruses only, and the original manufacturing process has already been validated for the removal of enveloped viruses, then it may be assumed that the original factor VIII or Factor IX product is safe with respect to removal/inactivation of hepatitis B virus, HIV 1+2 and hepatitis C virus and that the additional viral removal/inactivation step is designed to remove non-enveloped viruses such as hepatitis A and parvovirus B19. As most haemophilia patients are vaccinated against hepatitis A, clinical follow-up of these patients is difficult. The high incidence of parvovirus B19 seroconversion in all age groups makes it very difficult to assess the infectivity of the product with respect to parvovirus B19. No clinical trials testing parvovirus B19 seroconversion are mandatory before authorisation. After authorisation it is recommended that parvovirus B19 seronegative patients should be tested by gene amplification methods one week after the first treatment. Serum should be stored at -70°C for future testing.

Immunogenicity

The currently available factor VIII preparations differ with respect to purity and method of viral removal/inactivation. Until recently, the evidence supporting the notion that a particular production process is associated with a higher than normal risk of inhibitor induction has been very limited. Nevertheless some products do cause a higher incidence inhibitors than others. The clusters of inhibitors after infusion of factor VIII CPS-P in previously treated patients in 1991, illustrate the necessity to perform immunogenicity trials. Such inhibitors will be demonstrable in previously treated patients.
3.3 Clinical trials with factor VIII products

3.3.1 Pre-Authorisation

3.3.1.1 Efficacy

A comparative pharmacokinetic trial, measuring half-life and recovery, should be performed in at least 12 subjects with haemophilia A (factor VIII <2%). Patients should be at least 12 years of age without inhibitor and not actively bleeding and should not have received an infusion of concentrate in at least the past 3 days (if possible 7 days). As comparative product the currently authorised factor VIII product should be used. Samples for factor VIII activity determination should be taken before injection of 25-50 IU/kg of the new factor VIII product and between 15 and 30 minutes, 1, 3, 6, 9, 12, 24, 30-36 hours after the infusion. A minimum of 3 days (if possible 7 days) should be maintained between infusions. At least 3 different lots should be employed in the trial. Recovery should be determined from the peak factor VIII activity in the first four samples time periods post-infusion.

Patients who participated in the pharmacokinetic trial should continue treatment with the product for 6 months and at least 5 patients should be tested again for half-life and recovery after 3-6 months.

After administration of the factor VIII product in any patients treated with surgical procedures, response will be determined by the physician, including achievement of haemostasis, loss of blood and requirement of transfusions.

3.3.1.2 Safety

3.3.1.2.1 PTP Study

A minimum of 30 immunocompetent (CD4 lymphocytes > 400/ml) previously treated patients with severe haemophilia A with at least 10 exposure days to the new factor VIII product and a follow up of at least 6 months for all patients must be included prospectively. The factor VIII inhibitor titre will be determined every 3 months. The titre of the inhibitor should be reported (BU) as well as the clinical relevance, the cumulative incidence and the number of exposure days (also in relation to development of inhibitors). The follow up of these patients should be in accordance with EC Good Clinical Practice. The SPC should include a section stating the experience with respect to immunogenicity in PUPs or state that there is no such experience.

3.3.1.2.2 PUP Study

PUP studies should be carried out, or at least initiated. At the date of implementation of the modified manufacturing process, the SPC should state the experience with respect to immunogenicity in PUPs or state that there is no such experience. The PUP study should be done only after results of the PTP trials are available and according to the guideline (see 2.3.1.2.1) including at least 20 patients.

3.3.2 Post-Authorisation

3.3.2.1 PTP

After authorisation laboratory parameters (according to the table in the appendix) from at least 50 PTPs treated for at least 2 years should be included in the Periodic Safety Update.

3.3.2.2 PUP

Immunogenicity and viral safety data (including parvovirus B19 seroconversion) on any PUPs treated with the product should be included in the Periodic Safety Update.
3.4 Clinical Trials with Factor IX Products

3.4.1 Pre-Authorisation

3.4.1.1 Efficacy

A comparative pharmacokinetic trial, measuring half-life and recovery, should be performed in at least 10 subjects with severe haemophilia B (factor IX ≤ 2%) patients should be at least 12 years of age and should not have received an infusion of concentrate in at least the past 4 days (if possible 7 days). As comparative product the currently authorised factor IX product should be used. Samples for factor IX activity determination should be taken before injection of 50-75 IU/kg of the new factor IX product and 30 minutes, 1, 3, 6, 9, 12, 24, 30, 36 and 50 hours after the infusion. A minimum period of 4 days (if possible 7 days) should be maintained between infusions. At least 3 different lots should be employed in the trial. Recovery should be determined from the peak factor IX activity in the first four samples time periods post-infusion.

Patients who participated in the pharmacokinetic trial should continue treatment with the product for 6 months and at least 5 patients should be tested again for half life and recovery after 3-6 months.

After administration of the factor IX product in any patient treated with surgical procedures, adverse events and response will be determined by the physician, including achievement of haemostasis, loss of blood and requirement for transfusions and occurrence of thromboembolic episodes.

3.4.1.2 Safety

3.4.1.2.1 PTP Study

A minimum of 12 immunocompetent (CD4 lymphocytes > 400/ml) previously treated patients with severe haemophilia B with at least 10 exposure days to the new factor IX product and a follow up of at least 6 months for all patients must be included prospectively. The factor IX inhibitor titre will be determined every 3 months. The titre of the inhibitor should be reported (BU) as well as the clinical relevance, the cumulative incidence and the number of exposure days (also in relation to the development of inhibitors). The follow up of these patients should be in accordance with EC Good Clinical Practice. In addition, appropriate tests for activation of coagulation after administration of the product should be carried out in the patients included in the pharmacokinetic trial (see 2.4.2.). If they undergo surgery, clinical evaluation of thrombosis should be undertaken by safe, objective means.

3.4.1.2.2 PUP study

PUP studies should be carried out or at least initiated, however due to the lower incidence of haemophilia B as compared to haemophilia A, the study should include at least 15 patients. At the date of the implementation of the modified manufacturing process, the SPC should include a section stating the experience with respect to immunogenicity in PUPs or state that there is no such experience. The PUP study should be done only after the results of the PTP trial are available.

3.4.2 Post-Authorisation

3.4.2.1 PTP

After authorisation laboratory parameters (according to the table in the appendix) from at least 30 PTPs treated for at least 2 years should be included in the Periodic Safety Update.
3.4.2.2 PUP

Immunogenicity and viral safety data (including parvovirus B19 seroconversion) on any PUPs treated with the product should be included in the Periodic Safety Update report.
APPENDIX 1

BIOCHEMICAL AND SEROLOGIC SURVEILLANCE IN HAEMOPHILIAC PATIENTS COMMENCING TREATMENT WITH THE FACTOR VIII AND FACTOR IX CONCENTRATE UNDER STUDY

<table>
<thead>
<tr>
<th>Month after commencing new concentrate</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
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<tr>
<td>Recovery of Factor VIII or Factor IX</td>
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<td>HIV I +II</td>
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<td>Parvo Virus B 19</td>
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</table>

In patients with a previously detected coagulation inhibitory antibody, surveillance will be carried out at monthly intervals for the first three months following by 3 monthly intervals for one year. In the second year controls will be sampled every 6 months, after which 12 month intervals will be employed.