Factor VIII Concentrate
Factor IX Complex (Coagulation Factors, II, VII, IX, X) Concentrate

Application for retention on the WHO Model List

From: Plasma Protein Therapeutics Association (PPTA)

1. Summary statement of the proposal for retention
   Factor VIII and Factor IX complex concentrates are necessary for the safe and effective treatment of life-threatening and debilitating haemorrhage in people with haemophilia (hereditary and acquired forms).

   The substitution-therapy with clotting factor concentrates did not only raise the life expectancy of people with Haemophilia from some 16 years up to normality, it enabled people with Haemophilia and their families to live a "normal" life and become active members of society.

   The use of alternative treatment, in the form of cryoprecipitate or fresh frozen plasma is considerably less effective as well as less safe.

   Removal of these product categories from the WHO Model List is likely to result in reduced availability of these life-saving medicines to people with haemophilia, followed by a decline in life expectancy and quality of life, not only in countries, where haemophilia treatment did not yet reach the adequate/minimal level of at least 1 international unit of Factor VIII per capita (according to data of the World Federation of Haemophilia). Their retention is therefore strongly requested on the grounds of public health.

2. Name of the focal point in WHO submitting or supporting the application
   Dr Neelam Dhingra, Acting Coordinator, Blood Transfusion Safety, WHO

3. Name of the organization(s) consulted and/or supporting the application
   European Haemophilia Consortium on behalf of 43 National Haemophilia Societies and Associations, representing some 40,000 families affected by Haemophilia in Europe
   World Federation of Haemophilia
   The International Society of Blood Transfusion (ISBT)

4. International Nonproprietary Name (INN, generic name) of the medicine
   Factor VIII concentrate
   Factor IX concentrate (complex or purified)

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group
   Therapeutic group

6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
   The US Center for Disease Control (CDC) estimates prevalence in the US to be between 97 and 205 cases per million in the male population, or approximately 75 cases per million total population. This therefore constitutes a 'rare disease' under the terms of the USA Rare Disease Act of 2002 (HR 4013) and the US Orphan Drug Act (700 per million), or of the European Commission’s definition (one affecting fewer than 500 per million).
However, the burden of disease is high and the condition is easily treatable. Average life expectancy in Europe prior to the development of effective treatment was in the mid teens. With effective treatment this has risen close to the figures for the normal male population. Reduction in joint damage allows people with haemophilia to lead normal, productive lives free of deformity.

Without factor concentrates people in the developing world either receive no treatment, or less effective treatments in the form of transfusions of blood or fresh frozen plasma, or cryoprecipitate. In addition to the relative lack of efficacy, these treatments bring with them the increased threat of transmission of HIV and Hepatitis viruses. Such transmission is no longer a problem with factor concentrates, since the introduction of effective viral removal and inactivation processes in the mid 1990s.

In conclusion, although classified as a rare disease, the fatal consequences of lack of treatment and the ease with which safe and effective treatment can be given with factor concentrates, mean that these concentrates should remain on the WHO Model List.

7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

Dosage information is given in a WHO document developed jointly with the World Federation for Hemophilia (WFH) and the International Society of Thrombosis and Haemostasis (ISTH):


The European Medicines Agency’s core Summaries of Product Characteristics (cSPC) for Factor VIII and Factor IX contain dosage information. The relevant sections are given as annexes to this document.

8. Summary of comparative effectiveness in a variety of clinical settings;

- Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data) / Summary of available data (appraisal of quality, outcome measures, summary of results) / Summary of available estimates of comparative effectiveness

The clinical evidence for the effectiveness of coagulation factors in the prophylaxis and treatment of bleeds in haemophilia has been extensively reviewed by regulators, the WHO and a wide range of other bodies.


For a discussion on the place of coagulation factor concentrates in haemophilia treatment in developing countries, see: Srivastava A. Factor replacement therapy in haemophilia--are there models for developing countries? Haemophilia. 2003 Jul;9(4):391-6.

9. Summary of comparative evidence on safety:

- Estimate of total patient exposure to date / Description of adverse effects/reactions / Identification of variation in safety due to health systems and patient factors / Summary of comparative safety against comparators

People with haemophilia have been treated with Factor VIII and Factor IX concentrates for many decades. Their safety profile is therefore well established.
The following text is taken from the EMEA core SPC for Factor VIII (CPMP/BPWG/1619/99, 29 June 2000):

As with any intravenous protein product, allergic type hypersensitivity reactions are possible (…) hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

(…)

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with <human> <recombinant> coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

Factor IX has a slightly different safety profile, and the core SPC (CPMP/BPWG/1625/99, 29 June 2000) contains the following text:

After repeated treatment with <human> <recombinant> coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX concentrates, the initial administrations of factor IX should, according to the treating physician’s judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Since the use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications, the risk being higher in low purity preparations, the use of factor IX-containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DEC). Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DEC. In each of these situations, the benefit of treatment with {Trade name of product} should be weighed against the risk of these complications.

Since the mid 1990s there have been no cases of transmission of HIV, Hepatitis B or Hepatitis C by factor concentrates manufactured using modern viral removal and inactivation manufacturing techniques.

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group;

- Range of costs of the proposed medicine

Prices for coagulation factor concentrates depend on a number of variables. In many countries prices are set by the health authorities. In others, tenders are used to supply health care needs. Prices may refer to ex-factory or final price payable by the user, or to prices at intermediate stages. The significance of the price is also affected by terms of
payment (some health care customers pay more than a year after delivery), compulsory rebates or price reductions etc.

With these caveats, it can be stated that figures derived from the Marketing Research Bureau’s Eurodata 2001 publication indicate a price range from US$0.25 to $0.73 per unit in 2001.

- Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

The health economic literature on the treatment of haemophilia with clotting factor concentrates is substantial. Given the life saving nature of on-demand coagulation factor treatment and the consequent clear pharmacoeconomic benefit of this mode of treatment, recent publications have tended to focus particularly on prophylaxis. See, for example: Miners AH, Sabin CA, Tolley KH, Lee CA. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Pharmacoeconomics. 2002;20(11):759-74. Such studies tend to conclude that primary prophylaxis is cost effective, but that this is sensitive to the protocols followed and the price of the clotting factor concentrate.

11. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

A broad range of Factor VIII and Factor IX concentrates have received regulatory approval in most countries of the world.


The British Pharmacopoeia also contains monographs for these coagulation factors.

13. Proposed (new/adapted) text for the WHO Model Formulary

It is proposed that the text in the WHO Model List of Essential Medicines remain substantially as at present but be modified to reflect the nature of current preparations:

<table>
<thead>
<tr>
<th>Complementary List</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII concentrate</td>
<td>Dried</td>
</tr>
<tr>
<td>Factor IX concentrate, purified</td>
<td>Dried</td>
</tr>
<tr>
<td>Factor IX complex (coagulation factors II, VII, IX, X)</td>
<td>Dried</td>
</tr>
<tr>
<td>concentrate</td>
<td></td>
</tr>
</tbody>
</table>
Annex 1
Dosage Guidelines for Factor VIII

from EMEA Core SPC for Human Plasma Derived and Recombinant Coagulation Factor VIII Products (CPMP/BPWG/1619/99) 29 June 2000

The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one mL of normal human plasma. The calculation of the required dosage of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by \(<x\% \text{ to } y\% \text{ of normal activity}> <x-y \text{ IU/dl}>\). The required dosage is determined using the following formula:

\[
\text{Required units} = \text{body weight (kg)} \times \text{desired factor VIII rise (\% (IU/dl))} \times \text{reciprocal of observed recovery}
\]

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in \(<\% \text{ of normal}\) \(<\text{IU/dl}>\) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor VIII level required (%) (IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20-40</td>
<td>Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30-60</td>
<td>Repeat infusion every 12-24 hours for 3-4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life threatening haemorrhages</td>
<td>60-100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30-60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80-100</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl)</td>
</tr>
</tbody>
</table>
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

[Where indicated in children, provide information on whether dose and frequency of administration differs. Where there are insufficient data to recommend use in children include the following:<There are insufficient data to recommend the use of {{trade} name of the product} in children less than 6 years of age>]

Patients should be monitored for the development of factor VIII inhibitors. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.
Annex 2
Dosage Guidelines for Factor IX

from EMEA Core SPC for Human Plasma Derived and Recombinant Coagulation Factor IX Products (CPMP/BPWG/1625/99) 29 June 2000

The dosage and duration of the substitution therapy depend on the severity of the factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma).

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one mL of normal human plasma. The calculation of the required dosage of factor IX is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by x% of normal activity. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) (IU/dl) x \{reciprocal of observed recovery\}

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. Factor IX products rarely require to be administered more than once daily.

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal <IU/dl>) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor IX level required (%) (IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20-40</td>
<td>Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30-60</td>
<td>Repeat infusion every 24 hours for 3-4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life threatening haemorrhages</td>
<td>60-100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30-60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>including tooth extraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>80-100 (pre- and postoperative)</td>
<td>Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30% to 60% (IU/dl)</td>
</tr>
</tbody>
</table>
During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

*For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days.*

*For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are \( \{x\} \) to \( \{y\} \) IU of factor IX per kilogram of body weight at intervals of \( \{x\} \) to \( \{y\} \) days.*

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Where indicated in children, provide information on whether dose and frequency of administration differs. Where there are insufficient data to recommend use in children include the following: *There are insufficient data to recommend the use of \{trade\} name of the product in children less than 6 years of age.*

Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor IX inhibitor is present. In patients with high levels of inhibitor, factor IX therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.