4. Place the product vial on an even and firm surface. Invert the diluent vial with the Mix2Vial set attached and push the spike of the transparent adapter and straight down through the product vial stopper. The diluent will automatically flow into the product vial.

5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the diluent-side and unscrew the set carefully into two pieces to avoid excessive foam building when dissolving the product. Discard the diluent vial with the blue Mix2Vial adapter attached.

6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

8. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.

9. Now that the concentrate has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe.

For injection of Factor X P Behring the use of plastic disposable syringes is recommended as the ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

Method of administration
– Administer slowly intravenously at a rate comfortable to the patient (max. 2 ml/min) via either intravenous injection using a suitable injection needle or intravenous infusion by means of a winged infusion set.
– It has to be taken care that no blood enters the syringe filled with product.
– Observe the patient for any immediate reaction. If any reaction takes place that is thought to be related to the administration of Factor X P Behring the rate of infusion should be decreased or the infusion stopped, as required by the clinical condition of the patient (see also “Special warnings and special precautions for use”).

UNDESIRABLE EFFECTS
Hypersensitivity or allergic reactions (which may include angioedema, stinging, burning (irritation), or phlebitis at the injection/infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently in patients treated with factor X/XI containing products. In some cases of haemophilia B, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also “Special warnings and special precautions for use”).

Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

In case of massive therapy the patient should be monitored for symptoms of hyperolemia.

On rare occasions, fever has been observed.

Patients may develop neutralising antibodies (inhibitors) to factor XIX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. In a clinical study in 14 previously untreated patients (PUPs) with hemophilia B no cases of development of inhibitors were reported.

There is a potential risk of thromboembolic episodes following the administration of factor X/XI products, with a higher risk for low purity preparations. The use of low purity factor X/XI products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism.

The use of high purity factor XIX is rarely associated with such side effects.

For information on viral safety see “Special warnings and special precautions for use”.

STORAGE AND STABILITY
Factor X P Behring is to be stored at +2 to +8 °C. Do not freeze.

Store in the closed carton!

Upon reconstitution, it is advisable to administer Factor X P Behring immediately; in any case the reconstituted solution should be administered within 8 hours to assure stability.

Keep out of the reach of children!

LICENSE NUMBER
47’726

On prescription only (3p)

DATE OF LAST REVISION
July 2010

References:
6. Perry DI, Factor X and its Deficiency States, Haemophilia, 3: 159-172; 1997

QUALITATIVE AND QUANTITATIVE COMPOSITION
Factor X P Behring is presented as a powder and solvent for solution for injection or infusion containing nominally 600 – 1200 IU human coagulation factor X and 620 IU human coagulation factor IX per vial.

The product reconstituted with 20 ml of water for injections contains approximately 30 – 60 IU/ml human coagulation factor X and 30 IU/ml human coagulation factor IX.

The specific activity of Factor X P Behring is 4 – 60 IU factor X/mg protein and 3 – 38 IU factor IX/mg protein.

Other ingredients
Antithrombin III, Heparin, Aminoacetic acid, calcium chloride, sodium chloride, sodium citrate, HCl or NaOH (in small amounts for pH adjustment)

Factor X P Behring does not contain a preservative.

Supplied solvent
Water for injections 20 ml

PHARMACEUTICAL FORM AND PRESENTATIONS
Pharmaceutical form
Powder and solvent for solution for injection or infusion.

Presentations
One pack with 600 – 1200 IU FX / 600 IU FIX containing:
1 vacuum vial with dried substance
1 vial with 20 ml water for injections
One device pack containing:
1 filter transfer device 20/20
1 disposable 20 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

PHARMACOTHERAPEUTIC GROUP
Antithrombotics: blood coagulation factor IX.

ATC code: B02B D04

NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER
CSL Behring AG
Wandtestrasse 10
3000 Bern 22
Switzerland

THERAPEUTIC INDICATIONS
Treatment and prophylaxis of bleeding in patients with
– haemophilia B (congenital factor IX deficiency)
– other diseases with factor IX- and/or factor X deficiency

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

High risk of thrombosis or disseminated intravascular coagulation (see also “Special warnings and special precautions for use”).

In case of recent thrombosis or recent myocardial infarction the risk of the therapy is to be weighed against that of non-treatment.
Dosage
The dosage and duration of the substitution therapy depend on the severity of the factor X/factor IX deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

F X deficiency:
Due to the rarity of the disease, no clinical studies with Factor X P Behring have been performed in subjects with FX deficiency. Therefore recommendations on dosage are based on information available in the literature (1–6), mainly data derived from treatment of FX-deficient subjects with plasma or prothrombin complex.

Dosage and duration of the substitution therapy depend on the severity of the factor X deficiency, on the location and extent of the bleeding. The amount to be administered should always be oriented to the clinical effectiveness in the individual case. One International Unit (IU) of Factor X activity is equivalent to that quantity of FX in one ml of normal human plasma. The calculation of the required dose of Factor X is based on the empirical finding that one unit FX per kg body weight raises the plasma factor X activity by approximately 1.5 % of normal activity. The required dosage is determined using the following formula:
Required units = body weight (kg) x desired factor X rise (% or IU/dl) x 0.7

Plasma levels between 10 to 40 % have been described as hemostatically effective (3–5). Based on the half-life of 24 to 40 hours, administration of FX every 24 hours should generally be sufficient if continued treatment in case of therapy failure is needed. Roberts & White (4) advise to avoid FX levels over 50 % due to the risk of thrombosis. During the course of treatment, appropriate determination of factor X levels is advised 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 X activity) is indispensable. Individual patients may vary in their response to Factor X, achieving different levels of in vivo recovery and demonstrating different half-lives.

Prophylactic treatment in infants and young children has been described in the literature, with up to 40 IU/kg of Prothrombin Complex Concentrates every 3 to 10 days (3) or 20 to 40 IU of Factor X per kg body weight once to twice a week (1, 2).

Factor IX deficiency:
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 is expressed 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 IU factor IX per kg body weight raises the plasma factor IX activity by 1.0 % of normal activity. The required dosage is determined using the following formula:
Required units = body weight (kg) x desired factor IX rise (% or IU/dl) x 1.0

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 (% of normal or IU/dl) in the corresponding period. The following tables 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 (% or 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 haemorrhosis, 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 haemorrhosis, muscle bleeding or haematoma</td>
<td>30 – 60</td>
<td>Repeat infusion every 4 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 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</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>