Dear Patient,
This leaflet gives you important information about this medicine. It is continually updated. Therefore, **please read this leaflet carefully**. Unfortunately, one cannot explain all the medical knowledge relating to your disease in such a small leaflet. This is why you might not understand every part of it without a comprehensive medical background or a personal explanation from your doctor. For this reason this leaflet also provides specialized information for your doctor, so that he can help you to understand.
If you have further questions about this medicine or any questions about your disease, please ask your doctor or pharmacist.

Factor X P Behring
Powder and solvent for solution for injection or infusion

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 (FX) and 600 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 ≤ 200 IU, Aminoacetic acid, Calcium chloride, Sodium chloride, Sodium citrate,
Sodium hydroxide (corresponding to 2.4 mmol or 56 mg sodium per vial), Hydrochloric acid

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
<u>One pack with 600 - 1200 IU FX / 600 IU FIX containing:</u>

1 vacuum vial with dried substance
1 vial with 20 ml water for injections
1 filter transfer device 20/20

One device pack containing:
1 disposable 20 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

PHARMACOTHERAPEUTIC GROUP

Antihaemorrhagics: blood coagulation factor IX.
ATC code: B02B D04

NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

CSL Behring AG,
Bern

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.

Present or past evidence of an allergic response to heparin, causing a fall in the number of blood platelets (Heparin-associated thrombocytopenia Type II, HAT Type II).

Pregnancy and lactation

Animal reproduction studies have not been conducted with factor X/IX. Based on the small number of patients with FX deficiency and the rare occurrence of haemophilia B in women,

experience regarding the use of Factor X P Behring during pregnancy and breast-feeding is not available. But single case reports from women with factor X deficiency indicate a positive effect of factor X substitution for the outcome of pregnancy (8).

Therefore, factor X/IX products should be used during pregnancy and lactation only if clearly indicated.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Factor X P Behring contains human proteins other than factor X or IX.

Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.

In case of shock, the current medical standards for shock-treatment should be observed.

After repeated treatment with human coagulation factor X/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 X/IX concentrates, the initial administrations of factor X/IX products 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 X/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 X/IX containing products may be potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC). 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 DIC. In each of these situations, the benefit of treatment with Factor X P Behring should be weighed against the risk of these complications.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents can not be totally excluded. This also applies

to pathogens of unknown nature. In order to prevent such infections the following standard measures have been taken:

- selection of donors,
- screening of individual donations and plasma pools for specific markers of infection,
- the inclusion of effective manufacturing steps for the inactivation/ removal of viruses.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Vaccination against hepatitis A and hepatitis B should be generally considered for patients in regular/ repeated receipt of human plasma-derived factor X/IX products.

It is strongly recommended that every time that Factor X P Behring is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Factor X P Behring contains up to 2.4 mmol (56 mg) sodium per vial, corresponding to 2.8 % of the WHO recommended daily intake of 2 g. To be taken into consideration by patients on a controlled sodium diet.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

No interactions of human coagulation factor X/IX products with other medicinal products are known.

Incompatibilities

This medicinal product must not be mixed with other medicinal products, except for normal saline.

DOSAGE AND ADMINISTRATION

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.

Dosage

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

<u>Factor X deficiency:</u>

Due to the rarity of the disease, no clinical studies with Factor X P Behring have been performed in subjects with factor X deficiency. Therefore recommendations on dosage are based on information available in the literature (1-6), mainly data derived from treatment of factor X-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 factor X 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 factor X 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 factor X every 24 hours should generally be sufficient if continued treatment is needed. Roberts & White (4) advise to avoid factor X levels over 50 % due to the risk of thrombosis. During the course of treatment, appropriate determination of factor X 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 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).

<u>Factor IX deficiency:</u>

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 actvity 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 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] × desired factor IX rise [% or IU/dl] × 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.

* reciprocal of observed recovery

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

Degree of haemorrhage/Type of surgical procedure	Factor IX level required (% or IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 – 40	Repeat every 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 – 60	Repeat infusion every 24 hours for 3 - 4 days or more until pain and acute disability are resolved.
Life-threatening haemorrhages	60 – 100	Repeat infusion every 8 - 24 hours until threat is resolved.
Surgery		
Minor including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved
Major	80 – 100 (pre- and postoperative)	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).

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 kg body weight at intervals of 3 to 4 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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.
See also section "Special warnings and special precautions for use".

There are insufficient data to recommend the use of Factor X P Behring in children less than 6 years of age.

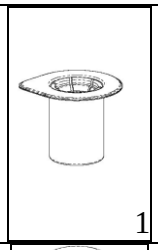
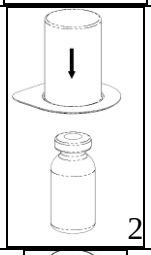
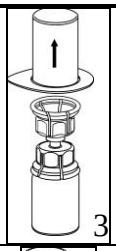
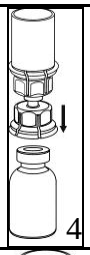
Overdose
No symptoms of overdose with human coagulation factor X or IX have been reported.

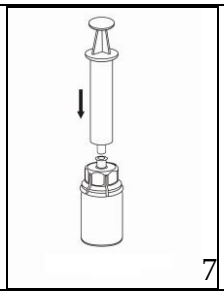
Administration

General instructions
- Do not use after expiry date given on the pack and container.
- The powder must be mixed (reconstituted) with the diluent (liquid) and withdrawn from the vial under aseptic conditions.
- The solution should be clear or slightly opalescent i.e. it might be sparkling when held up to the light but must not contain any obvious particles. After filtering or withdrawal (see below) the solution should be checked by eye for small particles and discoloration, before it is administered.
- Do not use the solution if it is visibly cloudy or if it contains flakes or particles.
- Any unused product or waste material should be disposed of in accordance with local requirements and as instructed by your doctor.

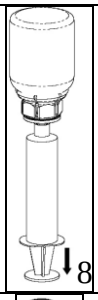
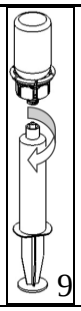
Reconstitution:
Without opening either vial, warm the Factor X P Behring powder and the solvent to room temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes. DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37 °C).

Carefully remove the protective caps from the diluent vial and the product vial. Clean the exposed rubber stoppers of both vials with one alcohol swab each and allow them to dry. The diluent can now be transferred to the powder with the administration set (Mix2Vial) attached. Please follow the instructions given below.

	1. Open the Mix2Vial package by peeling away the lid. Do **not** remove the Mix2Vial from the blister package!
	2. Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the diluent vial stopper.
	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
	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 end **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	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.

Withdrawal

	 8	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	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 or IX 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 hypervolemia.

On rare occasions, fever has been observed.

Patients may develop neutralising antibodies (inhibitors) to factor X or IX. 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/IX products, with a higher risk for low purity preparations. The use of low purity factor X/IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor X or IX is rarely associated with such side effects.

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 in order to assure sterility.

Keep out of the reach of children!

LICENSE NUMBER
47726
On prescription only (Rx)

DATE OF LAST REVISION

September2020

References:

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8. Kumar M, Mehta P. Congenital Coagulopathies and Pregnancy: Report of Four Pregnancies in a Factor X Deficient Woman. Am J Hematol, 46: 241-244; 1994