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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**CORE SPC FOR HUMAN PROTHROMBIN COMPLEX PRODUCTS  
(CPMP/BPWG/3735/02)**

<b>DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP</b>	June 2002 September 2002 February 2003 June 2003
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**CORE SPC  
FOR  
HUMAN PROTHROMBIN COMPLEX PRODUCTS**

*The QRD Product Information template with explanatory notes\* and the convention to be followed for QRD templates\*\* provide general guidance on format and text and should be read in conjunction with the core SPC and the Guideline on Summary of Product Characteristics.*

*In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the “Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products” (CPMP/BPWG/BWP/561/03).\*\*\**

\* <http://www.emea.eu.int/htms/human/qrd/qrdplt/H01a%20EN%20NOTE%20SPC-II-lab-pl%20v6.pdf>

\*\* <http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconventionv6.pdf>

\*\*\* <http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf>

## 1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name of product <strength, expressed as content of coagulation factor IX per container>  
<pharmaceutical form>}

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

*[Product specific information on quantitative composition as nominal potency per container and nominal potency per ml <after reconstitution>. Volume of solvent for reconstitution. Method of potency determination. Specific activity.]*

{(Invented) name of product} is presented as a {pharmaceutical form} containing human prothrombin complex. The product nominally contains the following IU of the human coagulation factors tabled below:

	Per container	After reconstitution with {z} ml of [define solvent]
	IU	IU/ml
Coagulation factor II	{ $\alpha$ }	{ $\kappa$ }
Coagulation factor VII	{ $\beta$ }	{ $\lambda$ }
Coagulation factor IX	{ $\gamma$ }	{ $\mu$ }
Coagulation factor X	{ $\delta$ }	{ $\nu$ }

The total protein content per {container} is {x} mg. The specific activity of the product is {y} IU/mg, expressed as factor IX activity, <before addition of other proteins>.

For excipients, see 6.1

## 3. PHARMACEUTICAL FORM

*[Product specific]*

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required
- Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor product is not available.

### 4.2 Posology and method of administration

#### Posology

Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-life of the different coagulation factors in the prothrombin complex (see section 5.2). Individual dosage requirements can only be identified on the basis of regular determinations of the individual plasma levels of the coagulation factors of interest, or on global tests of the prothrombin complex levels (prothrombin time, INR), and continuous monitoring of the clinical condition of the patient.

In case of major surgical interventions precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

**Bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment:**

The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (ml/kg body weight of the reconstituted product) required for normalisation of INR at different initial INR levels are given.

Initial INR	2-2.5	2.5-3	3-3.5	>3.5
Approximate dose ml/kg body weight	[product specific]	[product specific]	[product specific]	[product specific]

The correction of the vitamin K antagonist induced impairment of haemostasis persists for approximately 6-8 hours. However, the effects of vitamin K, if administered simultaneously, are usually achieved within 4-6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.

As these recommendations are empirical and recovery and the duration of effect may vary, monitoring of INR during treatment is mandatory.

**Bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when specific coagulation factor product is not available:**

The calculated required dosage for treatment is based on the empirical finding that approximately 1 IU of factor VII or factor IX per kg body weight raises the plasma factor VII or IX activity, respectively, by <0.01> IU/ml, 1 IU of factor II or X per kg body weight raises the plasma factor II or X activity by <0.02> and <0.017> IU/ml, respectively.

*[If product specific information on recovery in study populations is available the approximate figures given above should preferably be substituted by such data]*

The dose of a specific factor administered is expressed in International Units (IU), which are related to the current WHO standard for each factor. The activity in plasma of a specific coagulation factor is expressed either as a percentage (relative to normal plasma) or in International Units (relative to the international standard for the specific coagulation factor).

One International Unit (IU) of a coagulation factor activity is equivalent to the quantity in one ml of normal human plasma.

For example, the calculation of the required dosage of factor X is based on the empirical finding that 1 International Unit (IU) of factor X per kg body weight raises the plasma factor X activity by 0.017 IU/ml. The required dosage is determined using the following formula:

**Required units = body weight (kg) x desired factor X rise (IU/ml) x 60**

where 60 (ml/kg) is the reciprocal of the estimated recovery.

If the individual recovery is known that value should be used for calculation.

**Method of administration**

Dissolve the product as described at 6.6. {Invented name of the product} should be administered intravenously. *[A recommendation for maximal rate of injection/ infusion should be given].*

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients.

*[Product specific for products containing heparin]*

<Known allergy to heparin or history of heparin induced thrombocytopenia.>

#### 4.4 Special warnings and special precautions for use

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K dependent coagulation factors (e.g. as induced by treatment of vitamin K antagonists), {Invented name of the product} should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleeding or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient.

Patients receiving a vitamin K antagonist may have an underlying hypercoaguable state and infusion of human prothrombin complex may exacerbate this.

In congenital deficiency of any of the vitamin K dependent factors, specific coagulation factor product should be used when available.

If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of shock, standard medical treatment for shock should be implemented.

*[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]*

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency are treated with human prothrombin complex particularly with repeated dosing. The risk may be higher in treatment of isolated factor VII deficiency, since the other vitamin K dependent coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, close monitoring should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, to patients with liver disease, to per or post-operative patients, to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications.

*[Product specific]* <No data are available regarding the use of {(Invented) name of product} in case of perinatal bleeding due to vitamin K deficiency in the new-born.>

#### 4.5 Interactions with other medicinal products and other forms of interactions

Human prothrombin complex products neutralise the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known.

*[Product specific for products containing heparin:]*

<Interference with biological testing:

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken into account. >

#### 4.6 Pregnancy and lactation

The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established.

Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

#### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

Immune system disorders:

Replacement therapy may rarely lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.

Allergic or anaphylactic-type reactions have been <uncommonly><rarely>very rarely> observed.

General disorders and administration site conditions:

Increase in body temperature has been <commonly><uncommonly><rarely><very rarely> observed.

Vascular disorders:

There is a risk of thromboembolic episodes following the administration of human prothrombin complex. (see section 4.4).

*[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]*

## 4.9 Overdose

The use of high doses of human prothrombin complex products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. Therefore, in case of overdose, the risk of development of thromboembolic complications or disseminated intravascular coagulation is enhanced.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factors IX, II, VII, and X in combination, ATC code: B02BD01

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly called the Prothrombin Complex.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue factor-factor VIIa complex activates coagulation factors X and IX, whereby factor IXa and Xa are formed. With further activation of the coagulation cascade prothrombin (factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of the primary haemostasis.

Isolated severe deficiency of factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis. Isolated deficiency of factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia.

Acquired deficiency of the vitamin K dependent coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K dependent coagulation factors and a clinical bleeding tendency which, however, is often complex due to a simultaneous ongoing low-grade intravascular coagulation, low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

## 5.2 Pharmacokinetic properties

*[Product specific]*

*[A table providing half-life information should be included. (It may be acceptable that some of the data are provided from literature.)]*

Coagulation factor	half-life
Factor II	<i>[product specific]</i>
Factor VII	<i>[product specific]</i>
Factor IX	<i>[product specific]</i>
Factor X	<i>[product specific]</i>

## 5.3 Preclinical safety data

*[Product specific]*

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*[Product specific]*

<heparin: IU/IU FIX or IU/ml>

<antithrombin: IU/IU FIX or IU/ml>

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

<Only the provided <injection> <infusion> sets should be used because treatment failure can occur as a consequence of coagulation factor adsorption to the internal surface of some injection/infusion equipment.> *[If an injection/infusion set is not provided, information should be included on suitable injection/infusion sets].*

## 6.3 Shelf-life

*[Product specific]*

## 6.4 Special precautions for storage

*[Product specific]*

## 6.5 Nature and contents of container

*[Product specific]*

## 6.6 Instructions for use and handling and disposal

*[Product specific]*

*[Product specific: {Instructions for reconstitution including reconstitution time}]*

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. <Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.>

Any unused product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

*[Product specific]*

# 8. MARKETING AUTHORISATION NUMBER(S)

*[Product specific]*

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

*[Product specific]*

**10. DATE OF REVISION OF THE TEXT**

*[Product specific]*