

1. NAME OF THE MEDICINAL PRODUCT

Cofact 250 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cofact is presented as a powder and solvent for solution for injection containing human prothrombin complex. The product nominally contains the following IU of the human coagulation factors tabled below:

	Cofact 250 IU	After reconstitution* (IU/ml)
Active Ingredients		
Coagulation factor II	140 – 350	14 – 35
Coagulation factor VII	70 – 200	7 – 20
Coagulation factor IX	250	25
Coagulation factor X	140 – 350	14 – 35
Other Active Ingredients		
Protein C	111 – 390	11 – 39
Protein S	10 – 80	1 – 8

*After reconstitution with 10 ml of water for injections.

The total protein content per 250 IU vial is 130 – 350 mg. The specific activity of the product is ≥ 0.6 IU/mg, expressed as factor IX activity.

The activities of all coagulation factors as well as Protein C and S (antigen) have been tested according to the current WHO or European Pharmacopoeia standards.

Excipient(s) with known effect

After reconstitution, this medicinal product contains 125 – 195 mmol sodium/l, up to 44.8 mg sodium per 250 IU vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is of bluish colour. The solvent is a clear, colourless liquid, free of visible particles.

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 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 on 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, the targeted INR and body weight. In the following tables approximate doses required for normalisation of INR at different initial INR levels are given.

The dose tables represent general dosage guidelines only which cannot replace the individual assessment of dose for every single patient and a close monitoring of INR and other coagulation parameters during therapy.

Recommended doses of Cofact in ml to achieve a Target INR ≤ 2.1

Initial INR \ Body weight	7.5	5.9	4.8	4.2	3.6	3.3	3.0	2.8	2.6	2.5	2.3	2.2
50 kg	40	40	40	30	30	30	20	20	X	X	X	X
60 kg	50	50	40	40	30	30	30	20	X	X	X	X
70 kg	60	50	50	50	40	40	30	30	X	X	X	X
80 kg	60	60	60	50	50	40	40	30	X	X	X	X
90 kg	60	60	60	60	50	50	40	30	X	X	X	X
100 kg	60	60	60	60	60	50	40	40	X	X	X	X

Recommended doses of Cofact in ml to achieve a Target INR ≤ 1.5

Initial INR \ Body weight	7.5	5.9	4.8	4.2	3.6	3.3	3.0	2.8	2.6	2.5	2.3	2.2
50 kg	60	60	60	50	50	50	40	40	30	30	30	30
60 kg	80	70	70	60	60	60	50	50	40	40	40	30
70 kg	90	80	80	70	70	70	60	60	50	40	40	40
80 kg	100	100	90	90	90	80	80	70	60	50	50	40
90 kg	100	100	100	90	90	90	80	80	70	60	50	40
100 kg	100	100	100	100	100	90	90	80	70	70	60	50

The doses are calculated based on the factor IX concentration in Cofact, because of its relatively short half-life and low yield after infusion in comparison with the other coagulation factors in Cofact. It is assumed that a mean plasma concentration of factor IX $\geq 30\%$ is sufficient to attain an INR of ≤ 2.1 and $\geq 60\%$ to attain an INR of ≤ 1.5 . Calculated amounts are rounded off on multiples of 10 ml and an upper limit of 60

or 100 ml in total was set (see tables above). The target INR values are recommended by the Federation of Dutch Thrombosis Services and are of the same order as English and German recommendations.

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.

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.

Paediatric population

The safety and efficacy of the use of Cofact in paediatric patients have not been established.

Method of administration

For instructions on reconstitution of the medicinal product before administration, see section 6.6. Cofact should be administered intravenously.

It is recommended to administer the reconstituted product at a rate of approximately 2 ml per minute.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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), Cofact 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 vitamin K antagonists may have an underlying hypercoagulable 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.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and for non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against other 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).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

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 thrombo-embolic 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 thrombo-embolic events or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment should be weighed against the risks of these complications.

No data are available regarding the use of Cofact in case of perinatal bleeding due to vitamin K deficiency in the newborn.

Excipients

Cofact contains up to 448 mg sodium per 100 ml, equivalent to up to 22 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration for patients on a controlled sodium diet.

Paediatric population

There are insufficient data to recommend the administration of Cofact in children and adolescents.

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.

4.6 Fertility, 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. See section 4.4 for information on the risk of Parvovirus B19 infection in pregnant women.

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

Tabulated list of adverse reactions of Cofact.

The adverse reactions presented have been reported during clinical trials and during post-marketing use of Cofact. The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequency of the adverse reactions is defined according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequency of Adverse Reactions (ADRs).

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency
Immune system disorder	Anaphylactic reaction, hypersensitivity	Not known
Nervous system disorders	Cerebrovascular accident, dizziness	Not known
Cardiac disorders	Acute myocardial infarction	Not known
Vascular disorders	Thromboembolic events (embolism, deep vein thrombosis); see section 4.4	Common
	Hypothension	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, respiratory failure	Not known
Gastrointestinal disorders	Nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	Hyperhidrosis, pruritis, urticaria	Not known
General disorders and administration conditions	Infusion site redness, infusion site irritation, infusion site swelling	Not known
	Malaise	
Investigations	Hepatic function abnormal	Not known

Replacement therapy may lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibition occurs, the condition will manifest itself as a poor clinical response e.g., ongoing bleeding.

For safety information with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via <the Dutch pharmacovigilance centre LAREB, Website www.lareb.nl>.

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 the case of overdose, the risk of development of thrombo-embolic 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. In addition to the coagulation factors Cofact contains the vitamin K dependent coagulation inhibitors Protein C and Protein S.

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.

The further ingredients, the coagulation inhibitors Protein C and Protein S, are also synthesized in the liver. The biological activity of Protein C is enforced by the cofactor Protein S.

Activated Protein C inhibits the coagulation by inactivating the coagulation factors Va and VIIIa. Protein S as cofactor of Protein C supports the inactivation of the coagulation. Protein C deficiency is associated with an increased risk of thrombosis.

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

The plasma half-life ranges of the four coagulation factors that are present in Cofact are described in the literature:

<u>Coagulation factor</u>	<u>Half-life</u>
Factor II	40 - 60 hours
Factor VII	4 - 6 hours
Factor IX	18 - 25 hours
Factor X	30 - 60 hours

5.3 Preclinical safety data

No experimental animal studies have been carried out with Cofact apart from one study on rats into a possible hypotensive effect (which proved not to be present).

Toxicology studies have been carried out on experimental animals with TNBP and Tween 80. Cofact contains not more than 0.4 µg TNBP per IU of factor IX and not more than 4 µg Tween 80 per IU of factor IX. When Cofact is used at the recommended dose the amounts of TNBP and Tween 80 which a patient receives, remain well below the levels which proved harmful in animal experiments.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: trisodiumcitrate-dihydrate, sodium chloride, antithrombin ≤ 0.6 IU/ml.

Solvent: water for injections.

6.2 Incompatibilities

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

Cofact is compatible with polypropylene material. Treatment failure can occur as a consequence of coagulation factor adsorption to the internal surface of other injection/infusion equipment.

6.3 Shelf life

3 years.

After reconstitution, chemical and physical in-use stability has been demonstrated for 3 hours at 15 °C – 25 °C. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Within its shelf life, the product may be stored at or below 25 °C for up to 6 months prior to use. If not used during this period it must be discarded. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. The date when taken to room temperature should be marked on the package.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

250 IU of powder in a vial (type I glass) with a stopper (bromobutyl) + 10 ml of solvent in a vial (type I glass) with a stopper (bromobutyl) + a transfer needle – pack size of one.

6.6 Special precautions for disposal and other handling

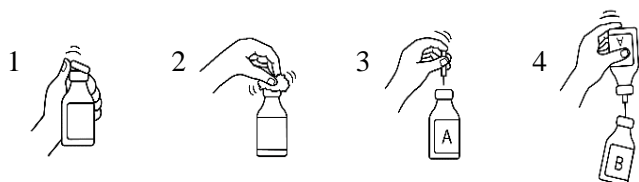
Dissolving

The dried protein fraction should be dissolved in the prescribed volume of water for injections. If stored at 2 °C – 8 °C it is necessary to bring the vials of Cofact and the water for injections to room temperature (15- °C – 25 °C) before dissolving the preparation.

Procedure using a transfer needle

1. Remove the plastic protective cap of both the vial containing the water for injections and the vial containing the product.
2. Disinfect the rubber stoppers of both vials with a piece of gauze soaked in alcohol (70%).
3. Remove the protective cover from one end of the transfer needle and insert the needle into the vial containing the water for injections (A).
4. Then remove the protective cover from the other end of the transfer needle, turn the vial containing the transfer needle upside down and immediately insert the needle that is still free into the vial containing product (B).

The negative pressure in the vial containing product will cause the water for injections to be sucked into the vial. Recommendation: while the water for injections is flowing across, the vial containing product should be kept tilted and the water allowed to flow along the wall of the vial. This helps to dissolve the product more quickly. As soon as all the water has flowed across, the emptied vial and the transfer needle should be removed in a single action.



In order to accelerate the dissolution process the vial may be gently swirled and, if necessary, heated to 30 °C. The vial should never be shaken nor should the temperature be allowed to exceed 37 °C. If the vial is heated in a water bath, care should be taken to ensure that the water does not come into contact with the protective cap and/or the rubber stopper.

As a rule, the dried substance should be fully dissolved within 10 minutes to form a blue-coloured solution; the blue colour is caused by the presence of the plasma protein ceruloplasmin.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Reconstituted product 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

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The Netherlands: 1 October 1997

10. DATE OF REVISION OF THE TEXT