1. NAME OF THE MEDICINAL PRODUCT

Cofact 500 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 500 IU	After reconstitution* (IU/ml)
Active Ingredients		
Coagulation factor II	280 – 700	14 – 35
Coagulation factor VII	140 – 400	7 – 20
Coagulation factor IX	500	25
Coagulation factor X	280 – 700	14 – 35
Other Active Ingredients		
Protein C	222 – 780	11 – 39
Protein S	20 – 160	1 – 8

**After reconstitution with 20 ml of water for injections.*

The total protein content per 500 IU vial is 260 – 700 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 89.6 mg sodium per 500 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 ≥ 30% is sufficient to attain an INR of ≤ 2.1 and ≥ 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥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 Hypothension	Common 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 Malaise	Not known
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:

Coagulation factor	Half-life
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

One package contains:

500 IU of powder in a vial (glass, Type I), closed with a rubber stopper (bromobutyl with fluorinated polymer coating) and an aluminium seal with a plastic flip-off cap

20 ml of solvent in a vial (glass, Type I), closed with a rubber stopper (bromobutyl with fluorinated polymer coating) and an aluminium seal with a plastic flip-off cap

1 transfer device nextaro v (15 µm filter nominal)

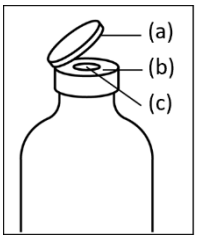
6.6 Special precautions for disposal and other handling

General instructions using a nextaro v transfer device

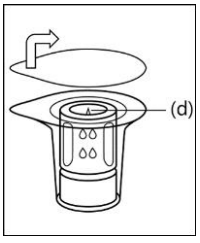
- The dried protein fraction should be dissolved with 20 ml water for injections. If stored at 2 °C - 8 °C it is necessary to allow the closed vials of powder and solvent (water for injections) to reach room temperature (15 °C - 25 °C) before dissolving the preparation. This temperature should be maintained during reconstitution. If a water bath is used for warming, care must be taken to avoid water coming into contact with the rubber stoppers or the flip-off caps of the vial. The temperature of the water bath should not exceed 37 °C.
- During the procedure described below, aseptic technique must be applied. Ensure the powder and solvent vial flip-off caps are removed and the collar rim and rubber stoppers are disinfected with an antiseptic solution and allowed to dry prior to opening the transfer device package. Do not touch the rubber stoppers of the solvent vial or the powder vial.
- As a result of the vacuum in the powder vial the solvent is automatically transferred into the powder vial.
- As a general rule, the powder should be fully dissolved within 10 minutes to form a blue-coloured solution. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. The solution 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.

Procedure using a nextaro v transfer device

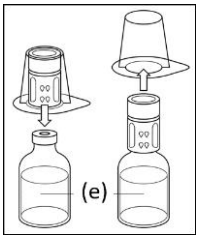
1. Remove the flip-off cap (a) from both the solvent vial and the powder vial. Disinfect the collar rim (b), including the rubber stopper (c), of both the solvent vial and of the powder vial with antiseptic solution



2. Open the transfer device package by peeling off the lid and remove the lid completely. To maintain sterility, do not remove the single-use transfer device from the package and do not touch the spike (d) of the transfer device.



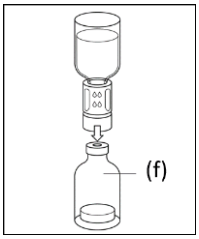
3. Place the solvent vial on an even and clean surface and hold it firmly with one hand. Without removing the outer package from the transfer device, place the blue part of the transfer device connector on top of the solvent vial (e) and press straight and firmly down until it snaps into place. Do not rotate the outer package while attaching.



4. While holding onto the solvent vial, carefully remove the outer package from the transfer device. Do not rotate the outer package and ensure to leave the transfer device attached firmly to the solvent vial

5. Place the powder vial (f) on an even surface and hold it firmly. Take the solvent vial with the attached transfer device and turn it upside down. Place the white part of the transfer device connector on top of the powder vial and press firmly down until it snaps into place. Do not rotate while attaching.

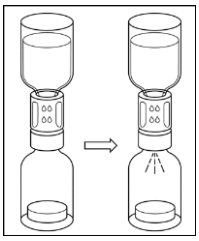
Note: The transfer device must be attached to the solvent vial first and then to the powder vial. Otherwise, loss of vacuum occurs, and transfer of the solvent does not take place.



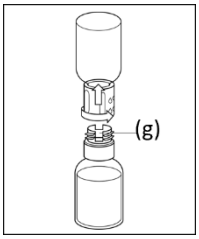
6. The solvent will flow automatically into the powder vial.

Wait until the solvent is completely transferred. Keep holding the entire unit consisting of solvent vial, transfer device and powder vial and make sure that it remains on an even surface during the entire transfer process.

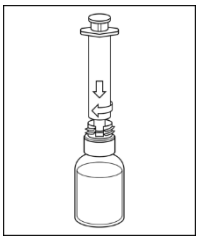
Once the solvent has been transferred, with both vials still attached, gently swirl the powder vial until the product is fully dissolved. To avoid foam formation, do not shake the vial.



7. After completing the transfer and dissolution of the preparation, hold the white part and rotate the connected blue part counterclockwise to unscrew into two parts. Remove and dispose the blue part along with the empty vial. Do not touch the Luer lock adapter (g).

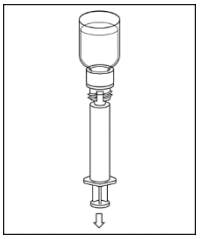


8. Hold the reconstituted vial firmly and attach a syringe (of at least 20 mL) to the Luer lock adapter (g) on the white part of the transfer device.



9. Turn the vial upside down and draw the solution into the syringe.

10. Once the solution has been transferred, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and remove the syringe from the white part of the transfer device. Dispose the white part along with the empty vial.



7. MARKETING AUTHORISATION HOLDER

Prothya Biosolutions Netherlands B.V.

Plesmanlaan 125

NL-1066 CX Amsterdam

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

In the Netherlands: RVG 17060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The Netherlands: 1 October 1997

10. DATE OF REVISION OF THE TEXT

7 August 2024