**Package leaflet: Information for the user**

**Cofact 500 IU powder and solvent for solution for injection.**

**Human prothrombin complex**

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes possible side effect not listed in this leaflet. See section 4.

**What is in this leaflet:**



## 1. What Cofact is and what it is used for

Cofact contains the active substances, factors II, VII, IX and X, which are human blood coagulation factors.

These factors are normal constituents of human blood and are commonly called the Prothrombin Complex. They are vitamin K dependent. If there is a deficiency of one or more of these factors, blood clotting disorders can occur. As a result of this, there is an increased tendency to bleed. The administration of Cofact serves to supplement this deficiency, thereby combating or preventing bleeding.

**Cofact can be used for:**

The treatment or prevention of bleeding, as the result of

- acquired deficiency of the prothrombin complex coagulation factors. For example, in cases of deficiency caused by the treatment with vitamin K antagonists or by an overdose of vitamin K antagonists, when acute correction of the deficiency is required.
- congenital deficiencies of one of the vitamin K dependent coagulation factors, when purified and specific coagulation factors are not available.

## 2. What you need to know before you use Cofact

**Do not use Cofact**

- If you are allergic (hypersensitive) to any of the active substances or other ingredients of this medicine (listed in section 6).

**Warnings and precautions**

Talk to your doctor specialized in clotting disorders before receiving Cofact.

- If you have an acquired deficiency of the vitamin K dependent clotting factors (for example caused by treatment with vitamin K antagonist medicines), 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, lowering the dose of the vitamin K antagonist medicine and/or administration of vitamin K is usually sufficient.
- If you receive vitamin K antagonist medicine, you may have an increased risk of forming blood clots. In this case, treatment with Cofact may enhance this risk.
- If you have been born with a deficiency of any of the vitamin K dependent clotting factors (congenital deficiency), specific coagulation factor products should be used when available.
- If an allergic or anaphylactic-type reaction occurs, the infusion of Cofact should be stopped immediately.

There is a risk of thrombosis or disseminated intravascular coagulation (i.e. formation of blood clots in blood vessels) when you receive Cofact, particularly when you receive it repeatedly.

- Your doctor will check whether the administration of Cofact poses a risk of thrombosis (see section 4, Possible side effects). The following individuals have a greater chance of developing thrombosis:
    - individuals who have suffered a heart attack or had (or still have) other diseases of the coronary arteries
    - individuals with liver diseases
    - newborn infants (neonates)
    - individuals who will soon undergo or have recently undergone surgery.
    - Individuals who are more likely to suffer from clotting complications (e.g. history of thrombo-embolic events or disseminated intravascular coagulation)

Your doctor will consider carefully the benefit of treatment with Cofact compared to the risk of these complications.

Viral Safety

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses and other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and 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 whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

It is strongly recommended that every time you receive a dose of Cofact, the name and batch number of the product are recorded in order to maintain a record of the batches used.

**Children and adolescents**

No data are available regarding the use of Cofact in children or adolescents.

**Other medicines and Cofact**

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

No information is available concerning possible interactions between Cofact and other medicines, with the exception of anticoagulants.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. If you are pregnant or breast-feeding, your doctor will give you Cofact only if it is clearly indicated.

**Driving and using machines**

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

**Cofact contains sodium**

Cofact contains up to 448 mg sodium (main component of cooking/table salt) per 100 ml. This is equivalent to up to 22 % of the recommended maximum daily dietary intake of sodium for an adult. Please take this into account if you are on a controlled sodium diet.

## 3. How to use Cofact

Your therapy should be initiated, administered and monitored by a doctor who is experienced in the treatment of coagulation disorders. Your doctor will determine the quantity of Cofact that you require for the treatment or prevention of haemorrhages as a result of using anticoagulants or in case of a congenital deficiency of one of the vitamin K dependent coagulation factors.

The exact dose is dependent on:

- the severity of your condition
- your weight
- the coagulation factors that you need
- the quantity of these factors in your blood (your blood level).

In case of congenital coagulation factor deficiency, it is important to regularly determine the blood levels of the coagulation factors.

Information for healthcare professionals is provided at the end of the leaflet.

**If you use more Cofact than you should**

Your doctor should regularly check your blood clot status during the treatment. High doses of prothrombin complex concentrate have been associated with instances of heart attack, disseminated intravascular coagulation and an increased formation of blood clots in a blood vessel in patients at risk of these complications.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been observed:

**Common** (may affect less than 1 in 10 people):
- There is a risk of formation of blood clots (see section 2)

**Uncommon** (may affect less than 1 in 100 people):
- There is a risk of drop in blood pressure

The frequency of the following side effects is **Not known** (frequency cannot be estimated from the available data):

- Hypersensitivity or allergic reactions (see section 2)
- Heart attack
- Nausea, vomiting
- Infusion site redness, infusion site irritation, infusion site swelling, malaise
- Temporary increase in liver test results
- stroke, dizziness
- Lung embolism, difficulty in breathing
- Excessive sweating, itchy skin, hives, rash

Patients with a deficiency of one of the coagulation factors II, VII, IX or X may develop antibodies against these factors as a result of using Cofact. In that case, the activity of the product will not be optimal.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via <the Dutch pharmacovigilance centre LAREB, Website www.lareb.nl>. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Cofact

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

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

Cofact can be stored at or below 25 °C up to six months. The date when taken to room temperature should be marked on the package. If not used during six months storage at room temperature the product must be discarded.

Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator.

The stability of the dissolved product has been demonstrated for up to 3 hours at 15 °C – 25 ºC. However, to prevent contamination, the dissolved product should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Cofact contains**

- The active substances are the coagulation factors II, VII, IX and X and further active substances are protein C and protein S.
- A vial of Cofact 500 IU contains 500 IU Factor IX; 280 – 700 IU Factor II; 140 – 400 IU Factor VII and 280 – 700 IU Factor X; 222 – 780 IU protein C; 20 – 160 IU protein S.

After being dissolved in the supplied water for injections, the ready made solution for injection contains:

- Not less than 14 IU and not more than 35 IU factor II per ml;
- Not less than 7 IU and not more than 20 IU factor VII per ml;
- 25 IU factor IX per ml;

- Not less than 14 IU and not more than 35 IU factor X per ml;
- Not less than 11 IU and not more than 39 IU protein C per ml;
- Not less than 1 IU and not more than 8 IU protein S per ml.

The other ingredients are trisodium citrate dihydrate, sodium chloride and antithrombin.

**What Cofact looks like and contents of the pack**

Cofact is supplied as a powder and a solvent for a solution for injection.

Cofact powder for injection is a bluish powder. The solvent is a clear, colourless liquid, free of visible particles. Ready made solution for injection is a bluish solution.

*Contents of the 500 IU pack*
1 vial 500 IU powder
1 vial 20 ml water for injections
1 transfer device nextaro v

Not all pack sizes may be marketed.

**Marketing authorisation holder and manufacturer**

Prothya Biosolutions Netherlands B.V.
Plesmanlaan 125
NL-1066 CX Amsterdam
The Netherlands

**This medicinal product is authorised in the Member States of the European Economic Area under the following names**:
Austria, Belgium, Finland, France, Germany, Iceland, Italy, Luxembourg, the Netherlands and Spain: Cofact.
Sweden: Thyaplex

**This leaflet was last revised in August 2024**

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The following information is intended for healthcare professionals only:

**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.

After reconstitution, this medicinal product contains 125 – 195 mmol sodium/l, up to 89.6 mg sodium per 500 IU vial.

**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. 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 "Special precautions for disposal and other handling". Cofact should be administered intravenously.

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

**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.

**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.

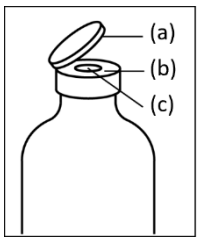
**Special precautions for disposal and other handling**

*General instructions using a nextaro v transfer device*

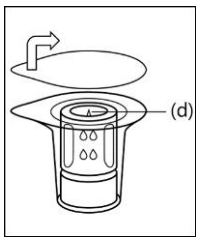
- The dried protein fraction should be dissolved with 20 ml water for injections. If stored at 2 °C - 8 °C it is necessary to allow the closed vials of powder and solvent (water for injections) to reach room temperature (15 °C - 25 °C) before dissolving the preparation. This temperature should be maintained 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*

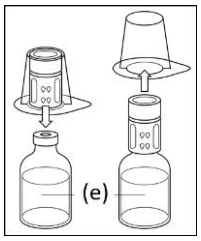
1. Remove the flip-off cap (a) from both the solvent vial and the powder vial. Disinfect the collar rim (b), including the rubber stopper (c), of both the solvent vial and of the powder vial with antiseptic solution




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.



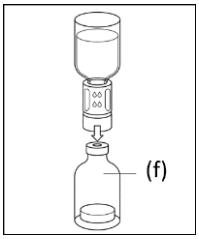

3. Place the solvent vial on an even and clean surface and hold it firmly with one hand. Without removing the outer package from the transfer device, place the blue part of the transfer device connector on top of the solvent vial (e) and press straight and firmly down until it snaps into place. Do not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

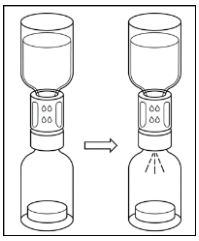
Note: The transfer device must be attached to the solvent vial first and then to the powder vial. Otherwise, loss of vacuum occurs, and transfer of the solvent does not take place.



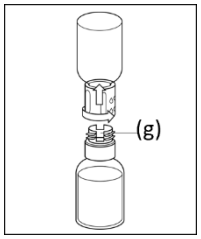

6. The solvent will flow automatically into the powder vial.

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.

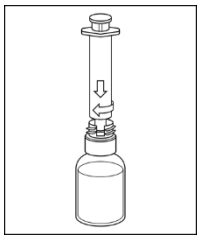
Once the solvent has been transferred, with both vials still attached, gently swirl the powder vial until the product is fully dissolved. To avoid foam formation, do not shake the vial.



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.