

## **Cofact 250 IU and 500 IU powder and solvent for solution for injection**

### **PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN**

#### **VI.2 Elements for a Public Summary**

##### ***VI.2.1 Overview of disease epidemiology***

Cofact contains four clotting factors (factors II, VII, IX and X) that are normally present in blood. Vitamin K is essential for the production of these factors by the liver. If a patient would need medication to make the blood thinner, often a medicinal product, a so called anticoagulant, is prescribed by a physician that counteracts the activity of vitamin K. As a result, the concentration of those four clotting factors becomes lower than normal and the blood clots slower. When a patient treated with such a product, a vitamin K antagonist, needs emergency surgery or in case of accidental bleeding the effects of the vitamin K antagonist must be reversed as quickly as possible. Since Cofact contains those four clotting factors, it is used to counteract the effects of a vitamin K antagonist in order to either prevent or to stop bleedings.

It is also possible that a patient has an inherited low concentration (congenital deficiency) of one of the four clotting factors in Cofact. Occasionally, patients with a congenital deficiency of one of the four clotting factors can have spontaneous or accidental bleedings that would not stop without medical treatment. If, for some reason, the specific clotting factor is unavailable, Cofact can be used as an alternative.

##### ***VI.2.2 Summary of treatment benefits***

The speed by which blood clots is expressed in the International Normalized Ratio (INR). For individuals who do not use anticoagulant medication the INR ranges between 0.8 to 1.2 (the normal value). When a patient is treated with a vitamin K antagonist the INR increases, which means that the blood clots at a lower speed. When such a patient needs to have the effects of a vitamin K antagonist reversed, the aim is to decrease that patient's INR. The INR does not necessarily have to become as low as the normal value. The treating physician will set a target INR to be reached by the administration of Cofact. It has been shown in a clinical study that the target INR was reached in 1 hour in 89% of patients when a dosage regimen based on body weight, initial INR and target INR was used. This dosage regimen is recommended in the SPC, currently.

##### ***VI.2.3 Unknowns relating to treatment benefits***

For Cofact no studies have been performed for specific groups such as pregnant or breastfeeding women, or children. However, since Cofact contains four clotting factors (factors II, VII, IX and X) that are normally present in blood, there is no reason to assume that treatment of those patients would result in different effects or that it would give cause to other safety concerns than those currently identified. To date, no adverse events have been reported after the use of coagulation factors in children or during pregnancy or breast-feeding. Nevertheless, Cofact should be used in those individuals carefully.

**VI.2.4 Summary of safety concerns**

**Important identified risks**

Risk	What is known	Preventability
<p>Acute serious allergic reaction (anaphylactic or hypersensitivity reaction)</p>	<p>As for all products that are made from human blood there is a small chance that a patient would have a (severe) allergic reaction after the administration of Cofact. Signs and symptoms of an allergic reaction are chest tightness, breathlessness and a low blood pressure. In scientific literature a case was reported on an assumed increased risk on allergic reactions in patients with IgA-deficiency <b>Error! Bookmark not defined..</b></p>	<p>If a patient is known to have an allergy to one of the components of Cofact, treatment should not be given.</p> <p>Patients with IgA-deficiency should use Cofact with caution, due to a possible increased risk for allergic reactions or anaphylactic reactions.</p> <p>During treatment with Cofact, the patient should be carefully monitored for signs and symptoms of an allergic reaction. If symptoms of an allergic reaction occur the treatment must be stopped immediately and the standard treatment for allergic reactions should be started.</p>
<p>Blood clots (thromboembolic events)</p>	<p>Because Cofact is meant to induce blood to clot there is a possible risk that a patient develops blood clots after treatment.</p> <p>Blood clots in the veins may lead to a painful swelling of the legs (deep vein thrombosis) and very occasionally life threatening or fatal clots in the lungs.</p> <p>In medical literature there are some reports on the development of blood clots that</p>	<p>To prevent blood clotting from happening, treatment with Cofact should only be initiated under the supervision of a physician experienced in the treatment of patients with clotting disorders. Also, precise instruction to estimate the optimal dose are given.</p>

Risk	What is known	Preventability
	<p>could potentially be caused by treatment with products such as Cofact or other products with similar components. It is assumed that the following patients might have a higher chance on developing blood clots:</p> <ul style="list-style-type: none"> <li>• individuals who have suffered a heart attack</li> <li>• individuals who have had (or still have) other diseases of the coronary arteries</li> <li>• individuals with liver diseases</li> <li>• newborn infants</li> <li>• individuals who have recently undergone surgery</li> </ul>	

#### Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
<p>Passing on infections (Transmission of infectious agents)</p>	<p>When medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. Therefore, 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, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include 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.</p>
<p>Development of inhibitors</p>	<p>On rare occasions, if a patient has an inherited very low concentration of one of the clotting factors II, VII, IX or X, it is possible that the body does not recognise such a factor as belonging to the patient's own body after Cofact is administered. As a consequence, the patient's defence system (immune system) might attempt to inactivate and remove that clotting factor from the blood. In such a situation the immune system generates so called inhibitors, but this can only happen when Cofact is</p>

Risk	What is known (Including reason why it is considered a potential risk)
	<p>administered repeatedly. Presence of inhibitors in a patient's blood may cause a reduced clinical effect of Cofact.</p> <p>There is no method to prevent the development of inhibitors. Still, it is recommended to administer, if available, the specific clotting factor the patient is lacking instead of Cofact.</p>
Off-Label use	<p>Cofact is only indicated as described in section <b>VI.2.1 Overview of disease epidemiology</b>. The use of Cofact in patients treated with rivaroxaban or dabigatran has been described in scientific literature. Rivaroxaban and dabigatran are so called Novel Oral Anticoagulants (NOACs) and they differ from the traditional vitamin K antagonists (VKAs) in that they can be administered in a fixed dose. For that reason NOACs do not require regular monitoring for dose adjustments unlike VKAs. However, as for any anticoagulant, NOACs can cause potential life threatening bleedings and need to be reversed in case of an emergency procedure. In the absence of a specific antidote, the immediate reversal of the anticoagulant effect could be achieved by administration of a prothrombin complex concentrate (PCC).</p>
Medication Errors	<p>Calculation and establishing the correct dose can be complex and incorrect dosing could lead to underdosing as well as overdosing of Cofact.</p>

### Missing information

Risk	What is known
<p>There is limited information on the use of Cofact in children, pregnant or breast feeding women, patients with a poor kidney function, patients with a poor hepatic function, or patients with a cardiac condition.</p> <p>Also, there is limited information on the use of Cofact in pregnant or breastfeeding women.</p>	<p>The 4 clotting factors in Cofact are natural constituents of human blood and function like normal clotting factors. Cofact is used to restore the levels of one or more of these clotting factors to normal concentrations in patients. Treatment with Cofact is therefore not expected to be associated with any safety concern. Nevertheless, Cofact should be used in those patients cautiously.</p> <p>Cofact should be used during pregnancy and lactation only if clearly indicated.</p>

#### ***VI.2.5 Summary of risk minimisation measures by safety concern***

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Cofact can be made available on request. This medicine has no additional risk minimisation measures.

#### ***VI.2.6 Planned post authorisation development plan***

No post-authorisation efficacy studies are planned by the MAH.

#### ***VI.2.7 Summary of changes to the Risk Management Plan over time***

This is the first Risk Management Plan.