PRODUCT MONOGRAPH

Beriplex® P/N 500 / Beriplex® P/N 1000

Powder and solvent for solution for injection
Human Prothrombin Complex

Factor II	380 - 800	IU / 760 – 1600 IU
Factor VII	200 - 500	IU / 400 – 1000 IU
Factor IX	500	IU / 1000 IU
Factor X	500 - 1020	IU / 1000 – 2040 IU
Protein C	420 - 820	IU / 840 – 1640 IU
Protein S	240 - 680	IU / 480 – 1360 IU

Ph. Eur.

ATC: B02BD01

Human Blood Coagulation factors II, VII, IX and X combination

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BERIPLEX® P/N 500 / BERIPLEX® P/N 1000

Human Prothrombin Complex

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous injection	Solvent and powder for solution / 500 IU or 1000 IU* * Factor IX is considered the lead factor for potency	Human antithrombin III, heparin, human albumin, sodium chloride, sodium citrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Beriplex® P/N 500 and Beriplex® P/N 1000, commonly known as Beriplex® P/N, are lyophilized plasma protein preparations containing all the essential vitamin K dependent human coagulation factors (Factors II, VII, IX and X) and the thrombo-inhibitor proteins C and S. Beriplex® P/N is available in two presentations: Beriplex® P/N 500 and Beriplex® P/N 1000. Factor IX is considered the lead factor for the potency of the preparation.

Since Beriplex® P/N is manufactured from human plasma, there is a risk that it may carry infectious agents. Therefore, standard measures are taken to prevent infections resulting from its use. These measures 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. Experiments were performed to evaluate selected manufacturing steps of the Beriplex® P/N manufacturing process for their capacity to inactivate or remove various viruses. The following manufacturing steps have been identified as having a significant potential for virus inactivation and/or removal: Pasteurisation (heat treatment in aqueous solution at 60°C for 10 hours) and virus filtration (20 nm filtration with 2 filters in series). Further manufacturing steps contribute to the overall virus reduction capacity: ammonium sulphate precipitation followed by calcium phosphate adsorption.

The results of the virus validation studies showed a very efficient and robust inactivation of the enveloped viruses studied and HAV through pasteurisation as well as an effective inactivation and robust removal of all viruses studied by virus filtration (see **PHARMACEUTICAL INFORMATION, Virus inactivation**).

INDICATIONS AND CLINICAL USE

Beriplex® P/N (Human prothrombin complex) is indicated in adults (≥ 18 years of age) for the 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.

No adequate study in subjects with congenital deficiency is available. Beriplex® P/N can be used for the treatment of bleeding and perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin K dependent coagulation factors only if purified specific coagulation factor product is not available.

Geriatrics (> 65 years of age):

The posology and method of administration in elderly people (> 65 years) is equivalent to the general recommendations.

Pediatrics (< 18 years of age):

No data is available regarding the use of Beriplex® P/N in the pediatric population.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section **Dosage Forms, Composition and Packaging**.
- In the case of disseminated intravascular coagulation, prothrombin complex-preparations may only be applied after termination of the consumptive state.
- Known history of heparin-induced thrombocytopenia.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The use of prothrombin complex concentrates is associated with the risk of thrombosis. Cases of thrombosis have been observed in conjunction with treatment with Beriplex® P/N (see Subsection General).

General

In patients with acquired deficiency of the vitamin K-dependent coagulation factors (e.g. as induced by treatment of vitamin K antagonists), Beriplex® P/N should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleedings 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 being treated with Vitamin K antagonists (VKA) therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event.

As reported with other PCCs, both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Beriplex® P/N in clinical trials and post-marketing surveillance. Monitor patients receiving Beriplex® P/N for signs and symptoms of thromboembolic events.

Beriplex® P/N was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Beriplex® P/N may not be suitable in patients with thromboembolic events in the prior 3 months.

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

If allergic or anaphylactic-type reactions occur, the administration of Beriplex® P/N has to be stopped immediately (e.g. discontinue injection) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed.

Beriplex® P/N contains up to 343 mg sodium (approximately 15 mmol) per 100 ml. This should be taken into consideration for patients on a controlled sodium diet.

Products manufactured from human blood or plasma present a risk of contamination by viruses such as HIV, hepatitis-causing viruses (HBV, HCV and HAV) as well as Parvovirus B19 (B19V). In theory, it is also possible for these products to transmit the agent responsible for the Creutzfeldt-Jakob disease (CJD) and the variant Creutzfeldt-Jakob disease (vCJD), i.e. the human equivalent of mad cow disease. The risk of transmission of prions, the causative agents of CJD/vCJD, through the use of Beriplex® P/N is negligible due to the fact that donors at risk of CJD/vCJD are excluded from blood donation permanently. Furthermore, studies using experimental TSE agents considered models for CJD and vCJD, have shown that some of the manufacturing steps of Beriplex® P/N are capable of removing prions in sufficient amounts so as to provide additional protection should these agents find their way in the plasma used as starting material for Beriplex® P/N. Stringent measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma have been put in place and include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of manufacturing steps for the effective inactivation/removal of viruses. However, despite these measures, the possibility of transmitting infectious agents cannot be totally excluded with regards to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and B19V.

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

It is strongly recommended that every time that Beriplex® P/N is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. All infections suspected by a physician to have been transmitted by this product should be reported to CSL Behring at 1-613-783-1892. The physician should discuss the risks and benefits of this product with the patient.

Hematologic

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 disseminated intravascular coagulation or thrombosis.

Because of the risk of thromboembolic complications, close monitoring should be exercised when administering Beriplex® P/N to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients pre- or postoperatively, to neonates or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency. In each of these situations, the potential benefit of treatment with Beriplex® P/N should be weighed against the potential risk of such complications. In patients with disseminated intravascular coagulation and sepsis antithrombin III substitution should be considered prior to treatment with Beriplex® P/N.

In patients with disseminated intravascular coagulation, it may, under certain circumstances, be necessary to substitute the coagulation factors of the prothrombin complex. This substitution may, however, only be carried out after termination of the consumptive state (e.g. by treatment of the underlying cause, persistent normalization of the antithrombin III level).

When Beriplex® P/N is used to normalize impaired coagulation, prophylactic administration of heparin should be considered.

Beriplex® P/N contains up to 2 IU/mL of heparin. Undesirable reactions may include the development of heparin-induced thrombocytopenia, type II (HIT, type II). Characteristic signs of HIT are a platelet count drop > 50 per cent and/or the occurrence of new or unexplained thromboembolic complications during heparin therapy. Onset is typically from 4 to 14 days after initiation of heparin therapy but may occur within 10 hours in patients recently exposed to heparin (within the previous 100 days).

Nephrotic syndrome has been reported in isolated cases following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.

No data is available regarding the use of Beriplex® P/N in case of perinatal bleeding due to vitamin K deficiency in neonates.

Beriplex® P/N has not been studied in patients with severe ischemic vascular disorder.

Special Populations

Pregnant and Nursing Women:

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.

Pediatrics (< 18 years of age):

No data is available regarding the use of Beriplex® P/N in the pediatric population.

Geriatrics (> *65* years of age):

The posology and method of administration in elderly people is equivalent to the general recommendations.

Monitoring and Laboratory Tests

Regular determinations of the individual plasma levels of the coagulation factors of interest, or global tests of the prothrombin complex levels (INR, Quick's test), as well as continuous monitoring of the clinical condition of the patient are necessary in order to assess a patient's individual dosage requirements.

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

A decrease of platelet count after the administration of Beriplex® P/N was observed in the clinical studies as well as the animal studies. The clinical relevance of this finding is unknown.

ADVERSE REACTIONS

Adverse Drug Reaction Overview (Safety Profile):

Allergic or anaphylactic-type reactions have been uncommonly observed, including severe anaphylactic reactions (see section "Warnings and Precautions, subsection General").

Replacement therapy may 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. In such cases, it is recommended to contact a specialized haemophilia center for guidance. Anaphylactic reactions have been observed in patients with antibodies to factors contained in Beriplex® P/N.

Increase in body temperature has been commonly observed.

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section "Warnings and Precautions, subsections General and Hematologic").

Lack of effect

The lack of effect is generally considered a listed/ expected adverse experience for any drug. Cases of lack of effect have been reported.

Tabulated list of adverse drug reactions of Beriplex

The following adverse reactions are based on clinical trial data, post-marketing experience* as well as scientific literature.

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been based on clinical trial data, 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) or not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Adverse Drug Reaction by PT**	**Frequency**
Vascular disorders and other SOCs	Thromboembolic events**	common
Blood and lymphatic system disorders	Disseminated intravascular coagulation	not known
Immune system disorders	Hypersensitivity or allergic reactions	uncommon
	Anaphylactic reactions including anaphylactic shock	not known
	Development of antibodies	not known
Nervous system disorders	Headache	common
General disorders and administration site conditions	Body temperature increased	common

**including cases with fatal outcome

* Post-marketing experience data has been collected since 1996, when the product was approved in Germany.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The evaluation of the safety of Beriplex® P/N is based on data from 3 clinical studies performed with Beriplex® P/N and on post-marketing experience data for the product. The 3 clinical studies were as follows:

- Efficacy study BE1116_3001
- Pharmacokinetics study BE1116_1001
- Efficacy study BE1116 / 7D–201KO

Table 1: Information on studies used for the safety assessment of Beriplex® P/N

Study number	Design	Dosage	Subject type
BE1116_1001	Prospective Open label Uncontrolled Single-center Phase I.	Single dose of 50 IU of factor IX per kg b.w.	Healthy subjects.
BE1116_3001	Prospective Open label Uncontrolled Multi-center Multinational Phase III.	Single dose of 25, 35, or 50 IU of factor IX per kg b.w. (depending on baseline INR).	Subjects with acquired deficiency of coagulation factors and requiring urgent reversal of oral anticoagulation.
BE1116 / 7D–201KO	Open label Uncontrolled Multi-center Phase II.	One or more doses, 1000–4000 IU Beriplex® P/N to adjust the Quick's value to 100% (INR of 1) for severe bleedings and before surgery or between 40 and 50% (INR of ≈ 1.6–1.9) for subjects under oral anticoagulation.	Subjects with acquired deficiency of coagulation factors II, VII, IX, and X (with pre-existing severe liver disease or treated with oral anticoagulation).

b.w.: body weight

A total of 81 subjects received one dose of Beriplex® P/N and 7 subjects received two doses of Beriplex® P/N during these studies. The safety data from the 3 studies have not been integrated, but rather are presented side-by-side. These data are quantitatively compared whenever possible. An overview of the safety parameters analysed in these studies is shown in **Table 2**.

Table 2: Safety variables analyzed in the studies

Safety Variables	BE1116_ 3001 (N=43)	BE1116_ 1001 (N=15)	BE1116 / 7D–201KO (N=30)
AEs	X	X	X
Hematology	X	X	X
Clinical chemistry	–	X	–
Thrombogenicity	X	X	X
Urinalysis	–	X	–
Virus safety	X	X	X
Vital signs	X	X	X
Physical exam	X	X	–

X = This safety variable was measured and reported for the study.

Table 3 presents a list of the adverse events (AEs) that were reported during these studies.

Table 3: Adverse events observed during studies used to assess Beriplex® P/N's safety

Adverse event (MedDRA Preferred Term)	Number (%) of subjects		
	BE1116_ 3001 (N=43)	**BE1116_ 1001 (N=15)**	**BE1116 / 7D–201KO (N=30)**
Abdominal pain	1 (2%)	-	-
Acute respiratory failure	1 (2%)	-	-
Angina pectoris	1 (2%)	-	-
Anxiety	1 (2%)	-	-
Back pain	1 (2%)	-	-
Cardiac death	1 (2%)	-	-
Cardiac arrest	-	-	-
Cardiac failure congestive	-	-	-
Cardiac valve disease	-	-	-
Cerebral artery embolism	1 (2%)	-	-
Cerebral haemorrhage	-	-	-
Chest pain	1 (2%)	-	-
Cough	1 (2%)	-	-
Duodenal ulcer hemorrhage	1 (2%)	-	-
Empyema	1 (2%)	-	-
Gastric cancer	1 (2%)	-	-
Hepatic failure	-	-	1 (3%)
Hepatitis A	-	-	3 (10%)
Hiccups	1 (2%)	-	-
Hyperchlorhydria	1 (2%)	-	-
Hypertension	2 (5%)	-	-
Insomnia	1 (2%)	-	-

Adverse event (MedDRA Preferred Term)	Number (%) of subjects		
	BE1116_ 3001 (N=43)	**BE1116_ 1001 (N=15)**	**BE1116 / 7D–201KO (N=30)**
Laboratory test abnormal	-	-	1 (3%)
Laryngitis	1 (2%)	-	-
Nausea	4 (9%)	-	-
Nasopharyngitis	-	2 (13%)	-
Oedema peripheral	1 (2%)	-	-
Pain in extremity	1 (2%)	-	-
Pancreatitis acute	-	-	-
Peripheral embolism	1 (2%)	-	-
Pleural effusion	1 (2%)	-	-
Procedural complication	1 (2%)	-	-
Prothrombin level abnormal	1 (2%)	-	-
Pruritus	1 (2%)	-	-
Pulmonary embolism	1 (2%)	-	-
Pyrexia	5 (12%)	-	-
Renal failure acute	1 (2%)	-	-
Septic shock	-	-	1 (3%)
Staphylococcal sepsis	-	-	-
Subdural hematoma	-	-	-
Suspicion of pulmonary infection	1 (2%)	-	-
Tracheal disorder	1 (2%)	-	-
Thrombotic stroke	-	-	-
Vomiting	2 (5%)	-	1 (3%)
Wound complication	7 (16%)	-	-

- = no AEs of that type occurred.

BE1116_3001 study

A total of 25 subjects experienced at least one AE, however, most of these AEs were symptoms related to surgery or perioperative factors. Only 2 AEs were assessed as related to Beriplex® P/N: the AEs labelled "pulmonary embolism" and "laboratory test abnormal". The subject who experienced abnormal laboratory test had abnormal prothrombin fragments 1 and 2 (F_{1+2}) levels immediately after infusion. This increase could at least partly be attributed to the content of Beriplex® P/N. These levels were already elevated above normal range before infusion, indicating that some activation of coagulation was already ongoing in this subject before the infusion of Beriplex® P/N.

The pulmonary embolism AE occurred in close timely relation with a second infusion of commercially available Beriplex® P/N and led to the death of the subject. Even though the embolism occurred shortly after the administration of Beriplex® P/N and was assessed as possibly related to the latter, other contributing factors (metastatic gastrointestinal cancer and arrhythmia absoluta) were also present in this case.

Four other subjects died due to AEs, one due to cardiac death, one due to renal failure acute, acute respiratory failure and empyema, a third one due to hemodynamic instability and the fourth one due to dyspnea, leucopenia, pleural effusion and cardiac decompensation. However, these deaths were assessed as not related to Beriplex® P/N.

BE1116_1001 study

Only 2 of the 15 subjects experienced AEs and both were unrelated to Beriplex® P/N.

BE1116 / 7D–201KO study

Seven out of 30 subjects experienced AEs in this study. Of all the AEs, only vomiting was considered related to Beriplex® P/N. Two patients died following an AE: one experienced hepatic failure and the other, septic shock. However, both deaths were related to underlying diseases and not to Beriplex® P/N treatment. The 3 AEs listed under Hepatitis A in table 3 relate to cases where seroconversion from anti-HAV negative to positive was observed. However, in all 3 patients, this seroconversion was not reflected by any clinical symptoms of hepatitis A infection during the study period. Furthermore, 2 of the patients became anti-HAV negative again after the treatment with immunoglobulins was ceased. The final assessment of the third patient could not be established as he was undergoing treatment with an immunoglobulin during the follow-up period. Samples of the Beriplex® P/N lot used to treat these patients were negative for HAV by NAT and it was thus determined that seroconversion was a result of anti-HAV antibodies transmission due to concomitant immunoglobulin therapy.

Other supporting clinical studies:

BE1116 / 7D–202KO study

The primary objective of this phase II clinical trial (prospective, open, uncontrolled, multi-center) was to demonstrate the capability of Beriplex® P/N to correct effectively the plasmatic coagulation defect in subjects with a congenital deficiency in FII, FVII, FIX, or FX. Only 2 subjects were included. No AEs occurred in either of the 2 subjects of this study.

Information from published medical articles:

Preston et al., 2002 (1) study

This medical article aimed to evaluate the efficacy and safety of Beriplex® P/N in patients requiring immediate reversal of their oral anticoagulation (warfarin). Forty-two subjects were enrolled in the study and received one single infusion of 25, 35, or 50 IU/kg body weight (b.w.) FIX, depending on baseline INR.

Adverse events were not described in this article. However, 8 subjects died within 7 days of being treated with Beriplex® P/N.

Of all the reported deaths, only one was assessed as possibly related to Beriplex® P/N. The subject in question experienced a thrombotic stroke 48 hours after receiving Beriplex® P/N to permit emergency leg amputation for severe atherosclerotic peripheral vascular disease. At the time of treatment this subject also had severe sepsis and both cardiac and renal failure.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events:

The number of deaths and serious adverse events was as expected for a study population comprising acutely and severely ill patients. Three (3) out of 43 patients in Study BE116-3001 and 2 out of 30 patients in Study BE1116 / 7D-201KO died within 7 days after receiving Beriplex® P/N. Four (4) of these 5 deaths were assessed as not related to administration of Beriplex® P/N. Only 1 of these 5 deaths, due to pulmonary embolism, was assessed as possibly related to Beriplex® P/N **(See Clinical Trial Adverse Drug Reactions)**.

Additionally, 2 deaths in Study BE1116-3001 occurred 1-6 months after receiving Beriplex® P/N. Both of these deaths were assessed as not related to Beriplex® P/N.

In the Preston's report (2002) (1), 8 patients died within 7 days after treatment with Beriplex® P/N. Seven (7) of these 8 deaths were assessed as not related to administration of Beriplex® P/N. Only 1 of these 8 deaths, thrombotic event, was assessed as possibly related to Beriplex® P/N.

In addition, 1 patient in Study BE1116-3001 experienced two arterial embolisms at 4 days and 7 days after receiving Beriplex® P/N. The outcome was unknown.

Deaths in Post-Marketing Cases: All of the reports with fatal outcome concerned patients with severe concomitant/ underlying diseases. In the majority of the spontaneously reported cases with fatal outcome, reversal of oral anticoagulation in acute emergency situations was the indication for Beriplex® P/N treatment. In these cases the underlying disease, which is the indication for anticoagulant therapy, leads to a prothrombotic state when anticoagulation is stopped. When anticoagulation is actively reversed with human prothrombin complex, externally applied coagulation factors add to the patient's intrinsic recovery of coagulation factors. It cannot be excluded that this temporarily contributes to an increase of the underlying prothrombotic vulnerability of the patient.

Abnormal Hematologic and Clinical Chemistry Findings

In the BE1116_3001 study, the subject who experienced abnormal laboratory test had abnormal prothrombin fragments 1 and 2 (F_{1+2}) levels immediately after infusion. This increase of F_{1+2} directly after infusion could at least partly be attributed to the content of F_{1+2} in Beriplex® P/N. The thrombin-antithrombin (TAT) complex and D-dimer levels of this subject were already elevated above normal range before infusion, indicating that some activation of coagulation was already ongoing in this subject before the infusion of Beriplex® P/N.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Beriplex® P/N neutralises the effects of vitamin K antagonist treatments.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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-lives of the respective 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 of interest, or on global tests of the prothrombin complex levels (INR, Quick's test), and a 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).

Recommended Dose and Dosage Adjustment

Bleeding and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.

The dose will depend on the International Normalised Ratio (INR) before treatment and the targeted INR. In the following table, approximate doses (ml/kg b.w. of the reconstituted product and IU of Factor IX/kg b.w) required for normalisation of INR (e.g. ≤ 1.3) at different initial INR levels are given.

Initial INR	2.0 – 3.9	4.0 – 6.0	> 6.0
Approximate dose ml/kg b.w.	1	1.4	2
Approximate dose IU (Factor IX)/kg b.w.	25	35	50

It is recommended that the maximum single dose should not exceed 5000 IU of factor IX. The correction of the vitamin K antagonist-induced impairment of haemostasis is reached at the latest 30 minutes after the injection and will persist for approximately 6 – 8 hours. However, the effect of vitamin K, if administered simultaneously, is usually achieved within 4 – 6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.

For patients weighing more than 100 kg the dose calculations have to be based on 100 kg b.w.

These recommendations are based on data from clinical studies with a limited number of subjects. Recovery and the duration of effect may vary, therefore monitoring of INR during treatment is mandatory.

Reconstitution and Administration

Beriplex® P/N should be reconstituted according to the instructions below.

Parenteral Products:

Reconstitution and withdrawal must be carried out under aseptic conditions.

Bring the Product and the solvent (diluent) to room temperature. Ensure that the product and solvent vial flip caps are removed and that the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial® package.

1. Open the Mix2Vial® package by peeling off the lid. Do **not** remove the Mix2Vial® from the blister package!

2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial® together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.

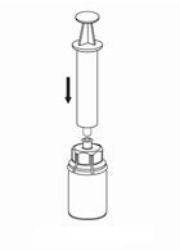
3. Carefully remove the blister package from the Mix2Vial® set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial® set.

4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial® set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.

5. With one hand grasp the product-side of the Mix2Vial® set, and with the other hand grasp the solvent-side and unscrew counterclockwise the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial® adapter attached.

6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial®´s Luer Lock fitting by screwing clockwise. Inject air into the product vial.



Withdrawal and application:

8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial® adapter from the syringe by unscrewing counterclockwise.

Beriplex® P/N must not be mixed with other medicinal products, diluents or solvents.

The solution should be clear or slightly opalescent. After filtering/withdrawal, the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.

Ensure that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots would therefore be administered to the patient. The reconstituted solution should be administered intravenously by a separate injection/infusion line (not more than 3 IU/kg/min, max. 210 IU/min, approximately 8 ml/min).

Because Beriplex® P/N contains no preservative; the reconstituted product should be used immediately to ensure its sterility. However, if it is not administered immediately, storage shall not exceed 3 hours at room temperature.

OVERDOSAGE

Overdosage with prothrombin complex concentrates has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The risk of thromboembolic complications or disseminated intravascular coagulation due to overdosage is increased in patients at risk of these complications. Regular monitoring of the coagulation status will help avoid overdosage.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

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 these coagulation factors Beriplex® P/N contains the vitamin K dependent coagulation inhibitors Protein C and Protein S.

Factor VII is the inactive enzyme precursor of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. Factor VIIa forms a complex with tissue thromboplastin which in turn activates coagulation factors IX and X, 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.

The other ingredients found in Beriplex® P/N, Protein C and Protein S, are also synthesized in the liver. The biological activity of Protein C is enforced by the cofactor Protein S. About 60% of the protein S is complexed to C4b binding protein (C4BP), presumably directing C4BP to cell surfaces at the site of injury. The remaining 40% of protein S functions as an anticoagulant co-factor for activated protein C in enhancing the inactivation of the pro-coagulatory factors Va and VIIIa in order to confine clot formation to the sites of vascular injury. Protein C deficiency is associated with an increased risk of thrombosis.

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 relevant bleeding tendency. However this is often complex due to a simultaneously 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.

Pharmacokinetics

Plasma half lives of the various components of Beriplex® P/N are presented in **Table 4**. The data was derived from a clinical study including 15 healthy volunteers.

Table 4: Half lives of the various components of Beriplex® P/N

Factor	$t_{½}$ median value (range)
Factor II	60 (25 – 135) hours
Factor VII	4 (2 – 9) hours
Factor IX	17 (10 – 127) hours*
Factor X	31 (17 – 44) hours
Protein C	47 (9 – 122) hours*
Protein S	49 (33 – 83) hours*

*terminal half-life; two-compartment-model

Absorption: Since Beriplex® P/N is administered intravenously, the preparation is available immediately; bioavailability is proportional to the dose administered.

Distribution: Beriplex® P/N is distributed in the organism in the same manner as the endogenous coagulation factors II, VII, IX and X.

Metabolism: Beriplex® P/N is metabolized in the same way as the endogenous coagulation factors II, VII, IX and X.

Excretion: Beriplex® P/N is excreted in the same manner as the endogenous coagulation factors II, VII, IX, X.

STORAGE AND STABILITY

Beriplex® P/N 500 and Beriplex® P/N 1000 can be stored either in the refrigerator or at room temperature (at +2°C to +25°C) for the period indicated by the expiration date printed on the carton and the vial label. The shelf life of Beriplex® P/N is 36 months. **Avoid freezing**, which may damage the solvent container. Keep Beriplex® P/N in its box during storage.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Beriplex® P/N is available in two presentations: Beriplex® P/N 500 / Beriplex® P/N 1000. It is supplied as a lyophilised powder (white or slightly coloured) in a single use vial along with a suitable volume of Sterile Water for Injection, Ph.Eur. provided as a solvent (diluent) (**Table 5**). The product package also includes a needle-less filter transfer device Mix2Vial® for the reconstitution and withdrawal of the product.

Table 5: Beriplex® P/N presentation

Beriplex® P/N presentation	Factor IX/Vial	Solvent (Diluent)
Beriplex® P/N 500	500 IU Factor IX/vial	Single vial of 20 mL
Beriplex® P/N 1000	1000 IU factor IX/vial	Single vial of 40 mL

Each vial of Beriplex® P/N contains the ingredients listed in **Table 6**.

Table 6: List of medicinal ingredients in Beriplex® P/N

Medicinal ingredients	Content after reconstitution (IU/mL)	Beriplex® P/N 500	Beriplex® P/N 1000
Factor II	20 - 48	380 – 800 IU/vial	760 – 1600 IU
Factor VII	10 - 25	200 – 500 IU/vial	400 – 1000 IU
Factor IX	25	500 IU/vial	1000 IU
Factor X	22 - 60	500 – 1020 IU/vial	1000 – 2040 IU
Protein C	15 - 45	420 – 820 IU/vial	840 – 1640 IU
Protein S	12 - 38	240 – 680 IU/vial	480 – 1360 IU

Beriplex® P/N also contains the following non-medicinal ingredients: Heparin, human antithrombin III, human albumin, sodium chloride sodium citrate and HCl or NaOH in small amount for pH adjustment. The components used in the packaging for Beriplex® P/N are latex-free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Human coagulation factors II, VII, IX and X, Protein C and Protein S
Molecular formula and molecular mass:	Factor II: ≈ 71.6 kDa Factor VII: 50 kDa Factor IX: 57 kDa Factor X: 58.8 kDa Protein C: 62 kDa Protein S: 69 kDa
Physicochemical properties:	Beriplex® P/N is available as a powder for solution which is soluble in water.

Product Characteristics

Beriplex® P/N is a lyophilized plasma protein preparation of the human prothrombin complex containing the blood coagulation factors II, VII, IX and X, as well as protein C and protein S. Factor IX is the lead factor for the potency of the preparation as stated on the label. The measured factor II potency is not less than 70 % and not more than 150 % of the measured factor IX potency. The preparation is sterile, pyrogen-free and does not contain any antimicrobial preservative.

Virus Inactivation

Because Beriplex® P/N is manufactured from human plasma pools there is a risk that it may carry infectious agents such as human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis A virus (HAV), as well as parvovirus B19 (B19V). Three principal complementary approaches are used to prevent the potential contamination of the final medicinal product:

- selecting and testing the source material for the absence of detectable viruses;
- testing the plasma pool for fractionation for the absence of contaminating infectious viruses;
- virus inactivation and removal by manufacturing steps from which selected steps are tested in virus validation studies for their capacity to inactivate and/or remove viruses.

Selection of the source material for the production of Beriplex® P/N with regard to minimal virus load is performed rigorously by selection of plasma centres, plasma donors and donations. Plasma collection centres are licensed and inspected by the competent authorities and audited by CSL Behring. The suitability of donors is confirmed by physical examination, intensive questioning (based on a pre-defined questionnaire) and a deferral policy. All donations are tested for serological markers (mandatory testing for hepatitis B antigen [HBsAg], antibodies against HIV-1, HIV-2 and HCV).

In addition, sample pools of donations are tested for the presence of genomic material of HAV, HBV, HCV, HIV-1 and high titres of B19V by NAT / PCR and reactive donations are interdicted. As a quality control measurement, only plasma pools for fractionation, which are negative for HBsAg and antibodies against HIV 1/2 and non-reactive for HAV RNA, HBV DNA, HCV RNA, HIV-1 RNA and high titres of B19V DNA, are released. The NAT / PCR testing complements donor selection and serological testing. Therefore, the plasma pools for fractionation may contain only very low levels, if any, of the transfusion relevant viruses HBV, HCV and HIV-1 as well as HAV. Furthermore, the plasma pool for fractionation has a limited load of B19V ($\leq$ 4 log10 IU B19V DNA/ml), which complements the virus reduction capacity of the manufacturing procedure to inactivate/remove B19V.

Experiments were performed to evaluate selected manufacturing steps of the Beriplex® P/N manufacturing process for their capacity to inactivate or remove various viruses. Throughout Beriplex® P/N's manufacturing process, the following steps have been identified as having an effective potential for virus inactivation and/or removal: Pasteurisation (heat treatment in aqueous solution at 60°C for 10 hours) and virus filtration (20 nm filtration with 2 filters in series). Further manufacturing steps contribute to the overall virus reduction capacity: ammonium sulphate precipitation followed by calcium phosphate adsorption. The step of ammonium sulfate precipitation was also validated for its virus reduction capacity.

The results of the virus validation studies showed an efficient and robust inactivation of enveloped viruses and HAV by pasteurisation as well as an effective and robust removal of all viruses studied by filtration. Furthermore, B19V was shown to be inactivated by pasteurisation by a mean reduction factor of 3.5 $\log_{10}$. It is therefore concluded that the manufacturing procedure of Beriplex® P/N provides a high margin of safety with regard to a wide range of viruses. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped viruses HAV and B19V.

CLINICAL TRIALS

Study demographics and trial design

Therapy with Beriplex® P/N is only indicated as replacement therapy in patients deficient in Factors II, VII, IX, and X. Therefore only one study in healthy human volunteers was performed, study BE1116_1001. The latter was designed to examine the pharmacokinetic (PK) properties of a single dose of Beriplex® P/N in healthy subjects.

Two clinical studies have been performed with Beriplex® P/N in individuals with an acquired deficiency of the coagulation factors of the prothrombin complex. The clinical studies were designed to assess the clinical efficacy, general clinical safety, and virus safety of the preparation. **Table 7** presents a summary of the key features of the abovementioned studies.

Table 7: Summary of patient demographics of Beriplex® P/N clinical studies

Study number	Design	Dosage	Study subjects (n=number)	Median age (range)	Gender
BE1116_1001	Prospective Open label Uncontrolled Single-center Phase I.	Single i.v. dose of 50 IU of Factor IX per kg b.w. over a period of about 19 min (≈ 200 IU/min).	Healthy subjects (n=15).	44 (18-62) years	7 F/ 8 M
BE1116_3001	Prospective Open label Uncontrolled Multi-center Multinational Phase III.	Single i.v. dose of 25, 35, or 50 IU of Factor IX per kg b.w. (depending on baseline INR) over a period of about 12 min (≈188 IU/min).	Subjects with acquired deficiency of coagulation factors and requiring urgent reversal of oral anticoagulation (n=43).	70 (22-85) years	22 F / 21 M
BE1116 / 7D–201KO	Open label Uncontrolled Multi-center Phase II.	One or more i.v. doses of 1000–4000 IU Beriplex® P/N to adjust the Quick's value to 100% (INR of 1) for severe bleedings and before surgery or between 40 and 50% (INR of ≈ 1.6–1.9) for subjects under oral anticoagulation. Administered over a period of about 10 min (≈ 236 IU/min).	Subjects with acquired deficiency of coagulation Factors II, VII, IX, and X with pre-existing severe liver disease (n=22) or treated with oral anticoagulation (n=8).	52 (29-88) years	9 F / 21 M

i.v. = intravenous; b.w. = body weight; INR = International Normalised Ratio; F = Female; M = Male

Based on total enrolment, 88 subjects (38 females, 50 males), were treated with Beriplex® P/N in the 3 studies. The subjects ranged in age from 18 to 88 years. The youngest study populations were the healthy subjects in study BE1116_1001. All of the subjects in the studies BE1116_1001, BE1116_3001 and BE1116 / 7D–201KO were Caucasian. In study BE1116 / 7D–201KO, the subgroup with liver disease was a younger population (median 45 years) than the subgroup receiving oral anticoagulation (median 77 years). The older subject populations with multiple concomitant diseases better reflect the overall disease population.

The intent to treat (ITT) population for each study was as follows: 43 subjects for study BE1116_3001 and 30 subjects for BE1116 / 7D–201KO.

Study BE1116_1001

For more information on this particular study, please refer to section **DETAILED PHARMACOLOGY**.

Study BE1116_3001

Study BE1116_3001 was undertaken to provide pivotal efficacy data for Beriplex® P/N in the reversal of coagulopathy in subjects treated with oral anticoagulants and who require immediate correction of their INR due to emergency surgery or acute bleeding.

The primary objective of this study was to demonstrate the capability of Beriplex® P/N to reverse effectively the oral anticoagulation effect by decreasing the INR values. The secondary objectives were to examine the capability of Beriplex® P/N to adequately increase the plasma levels of coagulation Factors II, VII, IX, X, Protein C, and Protein S to assess the cessation of spontaneously and traumatically induced bleedings or avoidance of excessive hemorrhages during and after emergency surgical interventions, as well as to evaluate its safety and tolerability.

Subjects received a single infusion of 25, 35, or 50 IU of Factor IX per kg b.w., depending on their baseline INR as follows:

Baseline INR	Dosage of Beriplex
2 – 3.9	25 IU of FIX per kg b.w.
4 – 6	35 IU of FIX per kg b.w.
> 6	50 IU of FIX per kg b.w.

INR, prothrombin time, Factor II, VII, IX and X activity, Protein C and Protein S were determined at baseline, 30 min, and 1, 3, 6, 12, 24, and 48 h after the end of the Beriplex® P/N infusion. Viral serology consisted of enzyme immunoassay testing of anti-HIV-1/HIV-2, anti-HCV, anti-HAV (IgG/IgM), anti-parvovirus B19 (IgG/IgM) antibodies, and HBsAg and polymerase chain reaction (PCR) testing of PCR parvovirus B19, PCR-HAV, PCR-HBV, PCR-HCV, and PCR-HIV. Tests were performed at baseline, and at Day 8–11 for anti-parvovirus B19, at 1 month after infusion for anti-parvovirus B19 (IgG/IgM) and anti-HAV (IgG/IgM), and at 3 months after infusion for anti-HCV, anti-HIV-1/-2, anti-HAV (IgG/IgM), and HBsAg.

Study BE1116 / 7D–201KO

The primary objective of study BE1116 / 7D–201KO was to demonstrate the capability of Beriplex® P/N to correct effectively the plasmatic coagulation defect in subjects with oral anticoagulation or severe liver disease. This was to be evidenced by: an adequate increase of the plasma level of Factors II, VII, IX, and X; normalization of the Quick's value and cessation of spontaneous and traumatic bleedings or avoidance of excessive hemorrhages during and after surgical or endoscopic interventions. Out of 30 subjects, 8 subjects had acquired deficiency of coagulation factors due to oral anticoagulation and 22 subjects had coagulation factors deficiency due to severe liver damage.

The secondary objective was to obtain further information about the tolerance of the intravenous administration of Beriplex® P/N.

23 Subjects received one dose and 7 subjects received two doses, in total 1000–4000 IU, of Beriplex® P/N to adjust the Quick's value to 100% (INR of 1) for severe bleedings and before surgery, or between 40 and 50% (corresponding to an INR of approximately 1.6–1.9) for subjects under oral anticoagulation. Factors I, II, V, VII, VIII, IX, X, Protein C, the Quick's value, and activated partial thromboplastin time (aPTT) were determined at baseline, 10, 30, and 60 min after the end of the Beriplex® P/N infusion. HBsAg, anti-HAV, anti-HBs, anti-HBc, anti-HCV, anti-HIV-l and anti-HIV-2 antibodies were to be assessed at baseline and 6 months after treatment with Beriplex® P/N.

<u>Other supporting clinical study:</u>

Study BE1116 / 7D- 202KO

The BE1116 / 7D 202KO study was designed as a supportive study to examine the clinical efficacy and safety of Beriplex® P/N in subjects presenting congenital deficiency in prothrombin factors. Only 2 patients with hemophilia B were included into this study. No valid conclusions can be drawn regarding efficacy and tolerance of treatment with Beriplex® P/N for the patient population with congenital deficiency of coagulation factors II, VII, IX and X.

Information from published medical articles:

Preston et al., 2002 (1)

This medical article aimed to evaluate the efficacy and safety of Beriplex® P/N in patients requiring immediate reversal of their oral anticoagulation (warfarin). Forty-two subjects were enrolled in the study and received one single infusion of 25, 35, or 50 IU/kg b.w. (b.w.) FIX, depending on baseline INR. The median baseline INR was 3.98. Complete INR correction (<1.3) was achieved in 20 min in 33 out of 42 subjects. The remaining 9 subjects had INRs of 1.30-1.90 within 20 min after receiving Beriplex® P/N.

Evans et al., 2001 (2)

This medical article aimed to determine the efficacy and safety of Beriplex® P/N in subjects presenting with an INR greater than 8.0 with major hemorrhage or requiring urgent surgery. Ten subjects received one single infusion of 30 IU/kg b.w. Factor IX. The median pre-treatment INR value was >20. All INRs measured 30 min after treatment were ≤1.3.

The international normalised ratio (INR)

INR is a coagulation test which is used to control the therapeutic effect of an oral anticoagulant. The test is based on the assay of the prothrombin time, which measures the time it takes plasma to clot after addition of tissue factor. The prothrombin time ratio is the prothrombin time divided by the result for control plasma. Due to the lack of a natural primary standard for the control plasma, harmonization was made possible by the adoption by the World Health Organization (WHO) of an international reference thromboplastin preparation. Each new commercial thromboplastin is calibrated against the primary WHO reference preparation. The results are used to calculate the relative sensitivity of the unknown preparation compared with the WHO standard International Sensitivity Index (ISI). The INR is calculated according to the formula:

$$INR = [\text{prothrombin time of sample} / \text{prothrombin time of control}]^{ISI}$$

Normalization of INR (i.e. ≤1.3 INR measured 30 minutes following an infusion) may be regarded as restoration of a normal coagulation system.

Investigator's assessment of treatment efficacy

In the majority of the studies presented here, investigators provided an assessment and/or judgement of the clinical efficacy of the Beriplex® P/N treatment in stopping ongoing bleeding or in avoiding excessive bleeding during surgical procedures. The scale and corresponding criteria used by the investigators were clearly predefined in study BE 1116_3001, which is presented in **Table 8**.

Table 8: Scale for investigator's judgement of adequacy of Beriplex® P/N treatment.

Category	Definition
Very good	Prompt cessation of bleeding and/or rapid fall in INR (≤1.3) Hemostasis during surgery clinically not significantly different from normal hemostasis.
Satisfactory	Delayed cessation of bleeding and/or delayed fall of INR (>1 to 2 hours) Mildly abnormal hemostasis during surgery in terms of quantity and/or quality – slight oozing.
Questionable	Cessation of bleeding and fall in INR >2 hours Moderately abnormal hemostasis during surgery – controllable bleeding.
None	Total lack of effect on bleeding and insufficient fall in INR Severely abnormal hemostasis during surgery in terms of quantity and quality – severe hemorrhage difficult to control.

Study results

Study BE1116_1001

For more information on this particular study, please refer to section **DETAILED PHARMACOLOGY**.

Study BE1116_3001

A rapid decrease in INR to ≤1.3 within 30 min after administration of Beriplex® P/N was achieved in 40 of 43 subjects (93%) in the ITT population. Three of 43 subjects (7%) did not have a rapid decrease of INR as defined per protocol. However, their 30 min post-infusion INR was 1.4 which, from a clinical point of view, can be considered almost normalized. The single infusion of Beriplex® P/N led to a direct increase of all plasma levels for Factors II, VII, IX, X, Protein C and Protein S reaching normal or near-normal median values.

In general 1 IU of Factor IX per kg b.w. can be expected to raise the plasma Factor IX activity by 1.3% (0.013 IU/mL) of normal; 1 IU Factor VII per kg b.w. raises the plasma Factor VII activity by 1.6% (0.016 IU/mL) of normal; and 1 IU Factor II or Factor X per kg b.w. raises the plasma Factor II or Factor X activity, respectively, by 1.8% (0.018 IU/mL) of normal. Approximately a 2% increase for each IU per kg b.w. can be expected for Protein C and Protein S.

Clinical efficacy was assessed by the investigators as very good in 40 of 43 (93%) of the subjects and satisfactory in 2 of 43 (5%) of the subjects. Thus Beriplex® P/N can be considered to have been effective for 42 of 43 (98%) of the subjects in this study. The investigator's assessment of treatment with Beriplex® P/N in the remaining subject was questionable, i.e. not effective. This subject was treated for bladder bleeding and suffered from a malignant bladder tumor, with a history of hematuria one week prior to inclusion in the study. The bleeding was most likely from malignant epithelium, and could not have been stopped through normalization of the coagulation system alone.

Study BE1116 / 7D–201KO

The median response and IVR of Factors II, VII, IX, X, and Protein C for the severe liver disease population, oral coagulant therapy population and overall population are summarised in **Table 9**.

Higher median response values in the oral anticoagulation group than in the liver disease group were observed for Factor II (1.4 vs. 1.3), Factor VII, (1.6 vs. 1.2) and Factor X (1.7 vs. 1.4). These differences are mainly due to the subjects' underlying diseases: subjects with chronic liver disease have a multiple coagulation defect and expanded plasma volume.

Table 9: Median efficacy parameters following the first treatment with Beriplex® P/N

Variable	Subject group	Median Response (range) (increase/dose/kg)	Median IVR (range) (%)
Factor II	Severe liver disease	1.3 (0.6 – 1.9)	52.6 (24.9 – 77.6)
	Oral anticoagulant	1.4 (1.0 – 2.9)	58.2 (41.8 – 118.4)
	All	1.3 (0.6 – 2.9)	54.3 (24.9 – 118.4)
Factor VII	Severe liver disease	1.2 (0.6 – 2.3)	49.7 (26.5 – 94.7)
	Oral anticoagulant	1.6 (1.1 – 3.7)	67.0 (47.0 – 152.6)
	All	1.3 (0.6 – 3.7)	52.4 (26.5 – 152.6)
Factor IX	Severe liver disease	1.4 (0.3 – 3.1)	56.5 (11.6 – 127.3)
	Oral anticoagulant	1.2 (0.7 – 4.0)	49.9 (28.0 – 162.1)
	All	1.3 (0.3 – 4.0)	55.2 (11.6 – 162.1)
Factor X	Severe liver disease	1.4 (0.7 – 2.4)	56.9 (27.1 – 99.3)
	Oral anticoagulant	1.7 (0.8 – 3.0)	69.3 (34.8 – 121.3)
	All	1.5 (0.7 – 3.0)	60.9 (27.1 – 121.3)
Protein C	Severe liver disease	1.4 (0.8 – 2.0)	57.4 (32.8 – 82.9)
	Oral anticoagulant	1.3 (0.9 – 1.9)	52.6 (36.5 – 78.8)
	All	1.4 (0.8 – 2.0)	56.7 (32.8 – 82.9)

Table 10 provides data on the Quick's value following the first treatment of subjects with Beriplex® P/N. Patients with oral anticoagulant received higher median dose of Beriplex® P/N compared to the patients with liver disease (3000 IU vs. 1500 IU). Higher maximal median Quick's values were observed in the oral anticoagulation group than in the liver disease group (87.1% vs. 63.0%). Moreover, the median response of the Quick's value for subjects with oral anticoagulation was considerably higher than that of subjects with liver disease (1.4 vs. 0.9). The Quick's value showed the expected increase after infusion of Beriplex® P/N in all subjects. The median response (increase/dose per kg) for the overall population was 1.0. The median response of subjects with oral anticoagulation was considerably higher than that of subjects with liver disease (1.4 vs. 0.9). Therefore, it would appear that an increase of the Quick's value by about 1% can be achieved with a lower dose of Beriplex® P/N in subjects taking oral anticoagulants than in subjects with liver disease. However, it should be taken into account that there were wide ranges for the response of the Quick's value in both the oral anticoagulation group (0.8–1.9) and liver disease group (0.4–1.9).

Table 10: Quick's value following the first treatment with Beriplex® P/N

Subject group	Median Baseline Level (range) (%)	Median Maximal Level (range) (%)	Median Response (range) (increase/dose/kg)
Severe liver disease	38.5 (23.0 – 91.0)	63.0 (46.0 – 120.0)	0.9 (0.4 – 1.9)
Oral anticoagulant	22.8 (13.0 – 58.7)	87.1 (60.0 – 97.7)	1.4 (0.8 – 1.9)
All	35.5 (13.0 – 91.0)	66.1 (46.0 – 120.0)	1.0 (0.4 – 1.9)

The clinical efficacy after the first treatment (29 evaluable subjects) was judged by the treating physicians as very good in 79% and satisfactory in 21% of the subjects, indicating 100% effective treatment. No differences were found between the oral anticoagulation group and the liver disease group with respect to this clinical judgment.

Study BE1116 / 7D–202KO

The response and IVR of Factors II, VII, IX, X and Protein C for both subjects were within the expected range (see **Table 11**). For both subjects, the Quick's value increased to 100% 10 min after the infusion of Beriplex® P/N and remained >80% up to the latest measurement performed (4 h after the infusion). Directly after the infusion, the aPTT values decreased from >60 sec to 40 sec and remained at this level throughout the observation period. The investigator judged the clinical efficacy at the end of the study as very good for both subjects. Since only two subjects with hemophilia B were enrolled, no formal conclusions can be drawn regarding efficacy of Beriplex® P/N in subjects with congenital deficiency of coagulation factors II, VII, IX, or X.

Table 11: Response and IVR of subjects following treatment with Beriplex® P/N

Variable	Patient	Response (increase/dose/kg)	IVR (%)
Factor II	01	1.7	70.4
	02	2.0	80.3
Factor IIV	01	0.9	35.7
	02	3.6	146.1
Factor IX	01	0.9	37.8
	02	2.0	82.8
Factor X	01	1.7	71.0
	02	2.3	93.9
Protein C	01	1.6	65.9
	02	2.0	80.3

Preston et al., 2002 (1) study

The median baseline INR was 3.98 (range 2.0–27.6). Complete INR correction (<1.3) was achieved in 20 min in 33 subjects. The remaining 9 subjects had INRs of 1.30–1.90 within 20 min after receiving Beriplex® P/N. Appropriate increases in Factors II, VII, IX, and X were observed in all subjects. Normal Protein C concentrations were achieved at 20 min in 36 of the 42 subjects.

Evans et al., 2001 (2) study

The median pre-treatment INR value was >20. All INRs measured 30 min after treatment were <1.3. At 30 min, 2 subjects had Factor VII levels less than 25 IU/dL (24.4 and 15.4 IU/dL, respectively). Every subject's levels of Factors II, IX and X were greater than 50 IU/dL. By 48 h, factor levels began to decrease slightly, and 5 subjects had an INR of 1.6 and one an INR of 1.7, indicating that 5 mg of intravenous vitamin K will not maintain complete correction of over anticoagulation in severely overanticoagulated subjects.

DETAILED PHARMACOLOGY

Study BE1116_1001 was designed to examine the pharmacokinetic (PK) properties of a single dose of Beriplex® P/N (50 IU of Factor IX per kg b.w.) in 15 healthy male and female subjects. The sample size was determined following the current Committee for Proprietary Medicinal Products (CPMP) note for guidance for plasma-derived FVIII and FIX products (8) in which at least 12 subjects are recommended for PK studies.

The activities of Factors II, VII, IX, X, Protein C and Protein S were determined before infusion of Beriplex® P/N and 5, 10, 15, and 30 min, and 1, 2, 3, 4.5, 6, 9, 12, 15, 18, 24, 32, 48, 72, 96, and 144 h after the end of infusion. A virus safety follow-up was also performed over a period of 12 weeks following the administration of Beriplex® P/N. The time points chosen were based on the half-lives observed in patients and reported in the literature (9,10) for Factors II, VII, IX, X and Protein C.

The PK parameters measured in this study included the incremental in vivo recoveries (IVRs) for Factors II, VII, IX, X, Protein C and Protein S; as well as their half-life, maximum concentration (C_{max}), area under the concentration-time curve (AUC), clearance, mean residence time (MRT), and steady-state volume of distribution (V_{ss}) values.

All 15 subjects who were enrolled completed the study. The median b.w. was 74.9 kg (range 58.6–94.5 kg); the median body mass index was 24.1 kg/m² (range 21.6–27.9 kg/m²).

Individual PK analyses were based on nonlinear regression models. All 15 subjects received the planned nominal dose of 50 IU Factor IX per kg b.w. Between 117 and 189 mL (median 150 mL) of reconstituted Beriplex® P/N was administered within 17 to 23 min (median 19 min).

Results

The in vivo recovery (IVR) was assessed by the incremental IVR (also called response), which describes the relationship between the increase in each Beriplex® P/N component level and the Beriplex® P/N component dose, standardized to 1 IU/kg b.w. The increase in each Beriplex® P/N component was defined as the difference between the maximum concentration of the Beriplex® P/N component during the 3 h after the start of Beriplex® P/N administration and the baseline component level before Beriplex® P/N administration. All maximum component levels occurred within the 3-h time interval. Median and mean incremental IVRs ranged between 1.6%/IU per kg b.w. for Factor IX and 2.8%/IU per kg b.w. for Protein C. The results for IVR are shown in **Table 12**.

Table 12: *In vivo* recovery of Factors II, VII, IX, X, Protein C and Protein S

Parameter	Median	Range	Mean (90% CI)	SD	CV (%)
Factor IX	1.57	1.11 – 2.59	1.64 (1.46 – 1.83)	0.40	25
Factor II	2.11	1.75 – 2.54	2.17 (2.05 – 2.28)	0.26	12
Factor VII	2.43	1.67 – 3.27	2.47 (2.28 – 2.67)	0.42	17
Factor X	2.08	1.64 – 3.19	2.16 (1.99 – 2.32)	0.36	17
Protein C	2.76	2.16 – 3.31	2.82 (2.67 – 2.97)	0.32	12
Protein S	2.02	1.46 – 2.70	1.99 (1.84 – 2.15)	0.34	17

CI = Confidence interval, CV = Coefficient of variation, SD = Standard deviation

The median incremental IVRs obtained in healthy subjects (study BE1116_1001) were to some extent higher than those obtained in the studies in patients (studies BE1116_3001, BE1116 / 7D–201KO and BE1116 / 7D–201KO) the clinical setting with subjects suffering from different (acute) illnesses certainly influences factor levels and recoveries.

Pharmacokinetic data for Factors II, VII, IX and X is presented in **Table 13** whereas data for Proteins C and S is presented in **Table 14**. Individual courses of each Beriplex® P/N component levels were adjusted for non-linear regression. Factors VII and X were adjusted according to a one-compartment model, and Factors IX, II, Protein C and Protein S were adjusted according to a two-compartment model. In general Factors IX, II, Protein C and Protein S showed a distribution phase.

Table 13: PK results for Factors II, VII, IX and X following administration of Beriplex® P/N

Parameters		Median	Range	Mean	SD	CV (%)
Factor II (N=15)	Initial half-life (h) (N=14)	6.2	2.3 – 11.4	6.2	2.4	39
	Terminal half-life (h)	59.7	25.0 – 135.3	60.4	25.5	42
	C_{max} (%)	238	195 – 265	235.7	21.5	9
	Dose-adjusted AUC (kg × h/dL)	102.8	59.9 – 211.3	113.7	36.3	32
	Clearance (mL/kg × h)	1.0	0.5 – 1.7	1.0	0.3	29
	MRT (h)	81.7	36.1 – 185.8	82.0	34.2	42
	V_{ss} (mL/kg)	71.0	47.5 – 101.0	71.4	13.7	19
Factor VII (N=15)	Terminal half-life (h)	4.2	2.1 – 9.2	5.0	1.9	38
	C_{max} (%)	170	118 – 203	165	22.5	14
	Dose-adjusted AUC (kg × h/dL)	14.2	5.7 – 34.7	17.1	8.3	49
	Clearance (mL/kg × h)	7.1	2.9 – 17.6	7.4	4.1	55
	MRT (h)	6.1	3.0 – 13.3	7.1	2.7	38
	V_{ss} (mL/kg)	41.8	29.2 – 68.8	45.0	10.7	24
Factor IX (N=15)	Initial half-life (h) (N=12)	7.0	2.9 – 14.2	7.0	3.0	43
	Terminal half-life (h)	16.7	9.5 – 127.1	42.4	41.6	98
	C_{max} (%)	170	123 – 213	172.3	28.8	17
	Dose-adjusted AUC (kg × h/dL)	27.5	14.7 – 76.4	34.2	18.5	54
	Clearance (mL/kg × h)	3.6	1.3 – 6.8	3.7	1.6	44
	MRT (h)	21.6	13.3 – 161.2	47.3	49.5	105
	V_{ss} (mL/kg)	92.4	56.5 – 210.9	114.3	54.6	48
Factor X (N=15)	Terminal half-life (h)	30.7	16.9 – 43.8	31.8	8.7	27
	C_{max} (%)	263	228 – 380	273.4	39.1	14
	Dose-adjusted AUC (kg × h/dL)	80.2	57.1 – 117.0	82.5	20.7	25
	Clearance (mL/kg × h)	1.3	0.9 – 1.8	1.3	0.3	24
	MRT (h)	44.3	24.3 – 63.2	45.9	12.6	27
	V_{ss} (mL/kg)	56.1	39.3 – 65.2	55.5	6.7	12

SD = Standard deviation; CV = Coefficient of variation

Table 14: PK results for Proteins C and S following administration of Beriplex® P/N

Parameters		Median	Range	Mean	SD	CV (%)
Protein C (N = 15)	Initial half-life (h) (N=12)	6.7	4.7 – 8.7	6.8	1.0	15
	Terminal half-life (h)	47.2	9.3 – 121.7	49.6	32.7	66
	C_{max} (%)	278	225 – 320	273.8	30.8	11
	Dose-adjusted AUC (kg × h/dL)	91.0	30.6 – 180.5	93.2	45.2	49
	Clearance (mL/kg × h)	1.1	0.6 – 3.3	1.5	0.9	64
	MRT (h)	57.0	13.4 – 161.4	62.4	42.1	67
	V_{ss} (mL/kg)	62.9	43.9 – 109.3	62.2	17.4	28
Protein S (N = 15)	Initial half-life (h)	4.7	0.9 – 7.0	4.2	1.8	43
	Terminal half-life (h)	49.1	33.1 – 83.3	50.4	13.4	27
	C_{max} (%)	162	138 – 218	170.2	25.9	15
	Dose-adjusted AUC (kg × h/dL)	90.0	54.7 – 144.1	89.9	22.5	25
	Clearance (mL/kg × h)	1.1	0.7 – 1.8	1.2	0.3	25
	MRT (h)	69.2	45.3 – 113.5	70.3	18.3	26
	V_{ss} (mL/kg)	76.6	61.9 – 105.0	78.8	11.6	15

SD = Standard deviation; CV = Coefficient of variation

The distribution of Factors VII and X remained within plasma, whereas the distribution of Factors IX, II, Protein C and Protein S slightly extended beyond plasma. Elimination of Factor VII, and to a lesser extent Factor IX, was reflected by a more rapid clearance and a shorter half-life. Slower clearance and longer half-lives could be seen for Factor X and, considerably, for Factor II, Protein C and Protein S. With the exception of the data for Protein C, these values are in line with values reported in the literature (9-13).

The half-life of Protein C (after infusion of human plasma Protein C) reported in the literature is somewhat variable. Most commonly, short half-lives of 3 to 12 h have been reported, but values of up to 32 h have also been stated (10,11,14-24).

Although in some of these references only the Protein C antigen level was measured rather than the activity, the correlation of antigen and activity has been shown by Baliga and coworkers (15), with the activity being somewhat lower than the antigen. In most of the publications the measurements did not go beyond 24 h after infusion. In some, the duration of blood sampling was not stated. Furthermore, several publications report data from one or two subjects only; and in the two papers reporting data from 7 and 30 subjects, respectively, these were subjects in a state of consumption of Protein C due to acute meningococcal sepsis and disseminated intravascular coagulation.

Okajima and coworkers (21) reported the half-life of a Protein C concentrate in 8 healthy subjects which would be a comparable setting to study BE1116_1001. They described a biphasic decay curve and calculated a mean plasma half-life of 10.9 h. However, they only tested Protein C levels until 24 h after infusion when the baseline levels had not yet been reached again. In study BE1116_1001, a biphasic distribution has also been seen with a median initial half-life of 6.7 h which is in accordance with the half-lives reported in the literature. However, due to the fact that the Protein C levels had not reached the baseline levels after the last blood sampling, a rather long median terminal half-life of 47 h was determined.

In general, it was only possible to estimate consistently the PK parameters for Factor X, whereas PK parameters for Factors II, VII, IX, Protein C and Protein S showed a high degree of variation. High interindividual variability of PK parameters is, however, not unexpected for human plasma proteins (25).

Conclusions

The PK data from study indicates that a sufficient increase of plasma factor levels can be expected in subjects after a single infusion of Beriplex® P/N (50 IU Factor IX / kg b.w.). The rather short half-life of Factor VII might be the limiting factor when treating patients, and could possibly necessitate repeated infusions in order to maintain sufficient Factor VII plasma activity. This, however, could then lead to an accumulation of Factor II with its long half-life. Interestingly, the inhibitor of coagulation, Protein C, also showed a long half-life that could be an advantage in patients with prothrombotic risk factors.

TOXICOLOGY

Toxicological animal studies were performed with either Beriplex® P/N or its predecessor Beriplex® HS. The difference between the two products is the addition of a nanofiltration step in the manufacturing of Beriplex® P/N to reduce potential virus burden. The nanofiltration step is only designed as a second virus inactivation step, no changes in the product are expected. Therefore the animal studies performed with Beriplex® HS are also valid for Beriplex® P/N.

Single-dose toxicity studies

The i.v. single-dose toxicity of Beriplex® HS was evaluated in mice and rats. Three groups of five male and five female mice received a single intravenous injection of Beriplex® HS at a dose of 20, 60 or 200 IU/kg. A fourth group of mice received an isotonic saline solution and served as control group. Criteria evaluated for compound effects included survival, clinical signs, body weight data and gross pathology. All mice tolerated the intravenous injection of Beriplex® HS.

The 20 and 60 IU/kg doses were well tolerated whereas the 200 IU/kg dose induced mild signs of toxicity with one mouse died 4 days after injection.

The same study was carried out in rats as well except that the rats received Beriplex® HS at doses of 20, 50 or 100 IU/kg. All the rats tolerated the intravenous injection of Beriplex® and all the doses studied were well tolerated.

Three groups of 26 rats (13 male and 13 female each) received single i.v. doses of 50, 100 and 500 IU/kg b.w. Beriplex® P/N. A fourth group (8 male and 8 female) received isotonic saline and was used as control. For all groups 10 rats were allocated to the main study. The treatment groups were complemented by 16 animals for the assessment of toxicokinetics and the placebo group was complemented by 6 animals. During the observation period clinical signs, body weight, food consumption and survival was recorded. In addition coagulation, hematology, clinical chemistry and urinalysis were performed prior to necropsy. On day 5 after the treatment, the animals were sacrificed and subjected to a histopathological evaluation (including macroscopic changes at necropsy). Toxicokinetics was determined pre-dose and at 0.25, 1, 3, 8 hours, 1, 3 and 5 days after treatment. The no-observed-adverse-effect level (NOAEL) in this study was established at 100 IU /kg b.w.

Local tolerance studies

Two studies were conducted in the rabbit to assess the local tolerance of Beriplex®HS and Beriplex® P/N.

The first study was conducted in three groups of 8 rabbits (4 males and 4 females) who received Beriplex® HS at 100 IU/5 ml either as an intravenous (i.v.) or intra-arterial (i.a.) injection or at 2 IU/0.1 ml as a paravenous (p.v.) injection in the left ear. An isotonic saline solution was injected in the right ear in the same manner as the studied substance on the left ear and served as control.

Clinical signs during and after the injections were recorded and an histopathological analysis of the injection site was conducted 1 and 2 days after the i.v. or i.a. injections or 2 and 7 days after the p.v. injection.

Beriplex® HS caused slight to moderate tissue alteration up to 24 hours following its i.a., i.v. and 48 hours following its p.v. injection. Most of the animals had recovered from their local irritations by the end of the experiment and it was concluded that Beriplex® HS was moderately tolerable after i.v., i.a. or p.v. injection. One animal in the i.v. group presented with a thrombus. The latter was most likely due to a combination of blood vessel insult due to the injection itself and the high concentration of coagulation factors. It was therefore suggested that Beriplex® HS be administered as slow infusions.

In the second study, five male rabbits received a single 5 mL i.v. injection, containing 125 IU, of Beriplex® P/N into their right ear. An isotonic saline solution was injected under the same conditions in their left ear and served as control. Immediately after the injection and 3 days later, the injection sites were investigated and clinical signs recorded. Three days after the injection, a histopathological analysis of the injection site was conducted. Results showed that Beriplex® P/N was well tolerated following intravenous injection.

Other toxicity studies

A safety pharmacology study was performed with one male and one female beagle dog The effects of Beriplex® HS at a cumulative dose of 90 IU/kg b.w. (given as subsequent doses of 10, 20 and 60 IU/kg i.v. with 5 min. intervals) were evaluated. Cardiovascular, respiratory and clinical chemistry parameters were monitored over a 1 hour observation period.

Cardiovascular, respiratory, hematological (except a mild and reversible decrease of leukocyte and platelet numbers) and clinical chemistry parameters were not influenced by the treatment. In conclusion, Beriplex® HS was well tolerated in two beagle dogs up to a cumulative dose of 90 IU/kg b.w.

Two safety pharmacology studies with a cumulative dose of Beriplex® P/N of 350 IU/kg b.w. (25, 75 and 250 IU/kg i.v. with 5 min. intervals) were performed on a total of 24 (12 males and 12 females) beagle dogs. Possible effects on vital systems were evaluated by recording cardiovascular, respiratory and clinical chemistry parameters over a 1 hour observation period.

Cardiovascular parameters were not influenced by the treatment, except for an increase of systolic and diastolic blood pressure. This effect appeared not to be dose-dependent and is frequently observed in this type of studies following the application of high volumes. Thus it was concluded that Beriplex® P/N was well tolerated in beagle dogs at a cumulative dose of 350 IU/kg b.w.

Finally, a study on 12 beagle dogs (6 males and 6 females) was conducted to investigate the influence of Beriplex® P/N on the coagulation system. The animals were treated with a dose of 25 (group 2), 75 (group 3) and 250 (group 4) IU of Beriplex® P/N per kg b.w. intravenously. The control animals (group 1) were treated with the vehicle solution of Beriplex® P/N under the same conditions. The animals were monitored for 7 days after the administration of Beriplex® P/N or the vehicle.

Results showed that the administration of Beriplex® P/N evoked no signs of coagulation activation in the group treated with 25 IU/kg of Beriplex® P/N, a moderate one in the group treated with 75 IU/kg of Beriplex® P/N and a clear one in the group treated with 250 IU/kg of Beriplex® P/N. A clear sign of consumption of coagulation factors was not observed, since fibrinogen, Quick's value, antithrombin III and platelet count did not change significantly.

REFERENCES

1. Preston FE, Laidlaw ST, Sampson B, Kitchen S. Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. Br J Haematol. 2002;116(3):619-24.

2. Evans G and Luddington R. Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding. Br J Haematol 2001; 115(4):998-1001.

3. Park EL, Broadberry RE, Yates S, Ghevaert CJG, Boulton FE, Poole J. Dramatic anamnestic response in a patient with anti-CHIDO due to transfusion of PCC. Vox Sanguinis 2004; 87 (Suppl. 3):S17-S92A.

4. Sakka SG, Sendt W, Huettemann E. Omentuminfarkt und Portalvenenthrombose im Rahmen der Gabe von PPSB. (in German) Intensiv-und Notfallbehandlung 2005; 30(1):34-7.

5. Moondi P, Cordingley J, Pepper J. Successful use of recombinant factor VIIa for the management of severe haemorrhage after cardiac surgery. Br J Intensive Care 2004; 14(4):136-8.

6. Bagot CN, Cregg R, Patel RK, Shariff A, Arya P. Perioperative myocardial infarction in a patient receiving low-dose prothrombin complex concentrate. Thromb Haemost 2007; 98(5):1141-2.

7. White R, Rushbrook J, McGoldrick J. The dangers of prothrombin complex concentrate administration after heart surgery. Blood Coagul Fibrinolysis 2008;19(6): 609-10.

8. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on the investigation of human plasma derived factor VIII and IX products. October 2000; CPMP/BPWG/198/95 rev. 1.

9. Fickenscher K. Analysis of individual coagulation factors. In: Thomas L, editor. Clinical laboratory diagnostics - use and assessment of clinical laboratory results. 1st ed. Frankfurt/Main, Germany: TH-Books Verlagsgesellschaft; 1998. p. 607-9.

10. Friedman KD and Menitove JE. Preparation and clinical use of plasma and plasma fractions. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, editors. Williams hematology. 6th ed. New York: McGraw Hill; 2001. p. 1917-34.

11. Griffin JH. Control of coagulation reactions. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, editors. Williams hematology. 6th ed. New York: McGraw Hill; 2001. p. 1435-49.

12. Board and scientific advisory committee of the German Federal Chamber of Physicians. "Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten" [*Guidelines for therapy with blood components and plasma derivatives*]. 3rd ed. Cologne: Deutscher Ärzte-Verlag; 2003.

13. D'Angelo A, Vigano-D'Angelo S, Esmon CT, Comp PC. Acquired deficiencies of protein S: Protein S activity during oral anticoagulation, in liver disease, and in disseminated intravascular coagulation. J Clin Invest 1988; 81(5):1445-54.

14. Auberger K. Evaluation of a new protein-C concentrate and comparison of protein-C assays in a child with congenital protein-C deficiency. Ann Hematol 1992; 64(3):146-51.

15. Baliga V, Thwaites R, Tillyer ML, Minford A, Parapia L, Allgrove J. Homozygous protein C deficiency--management with protein C concentrate. Eur J Pediatr 1995; 154(7):534-8.

16. Dreyfus M, Masterson M, David M, Rivard GE, Müller FM, et al. Replacement therapy with a monoclonal antibody purified protein C concentrate in newborns with severe congenital protein C deficiency. Semin Thromb Hemost 1995; 21(4):371-81.

17. De Kleijn ED, de Groot R, Hack CE, Mulder PGH, Engl W, Moritz B, et al. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: a randomized, double-blinded, placebo-controlled, dose-finding study. Crit Care Med 2003;31(6):1839-47.

18. Fourrier F, Leclerc F, Aidan K, Sadik A, Jourdain M, Tournoys A, et al. Combined antithrombin and protein C supplementation in meningococcal purpura fulminans: a pharmacokinetic study. Intensive Care Med 2003; 29(7):1081-7.

19. Griffin JH. Clinical studies of protein C. Semin Thromb Hemost 1984; 10(2):162-6.

20. Lignell A, Siegbahn A, Stridsberg M, Pauksen K, Gedeborg R, Sjölin J. Low utilisation of unactivated protein C in a patient with meningococcal septic shock and disseminated intravascular coagulation. Acta Anaesthesiol Scand 2003; 47(7):897-900.

21. Okajima K, Koga S, Kaji M, Inoue M, Nakagaki T, Funatsu A, et al. Effect of protein C and activated protein C on coagulation and fibrinolysis in normal human subjects. Thromb Haemost 1990; 63(1):48-53.

22. Riess H, Binsack T, Hiller E. Protein C antigen in prothrombin complex concentrates: content, recovery and half life. Blut 1985; 50(5):303-6.

23. Sills RH, Marlar RA, Montgomery RR, Deshpande GN, Humbert JR. Severe homozygous protein C deficiency. J Pediatr 1984; 105(3):409-13.

24. Vukovich T, Auberger K, Weil J, Engelmann H, Knöbl P, Hadorn HB. Replacement therapy for a homozygous protein C deficiency-state using a concentrate of human protein C and S. Br J Haematol 1988; 70(4):435-40.

25. White GC 2nd, Shapiro AD, Kurczynski EM, Kim HC, Bergman GE, the Mononine Study Group. Variability of in vivo recovery of factor IX after infusion of monoclonal antibody purified factor IX concentrates in patients with hemophilia B. Thromb Haemost 1995;73(5):779-84.

PART III: CONSUMER INFORMATION

Beriplex® P/N 500/ Beriplex® P/N 1000
Human Prothrombin Complex

This leaflet is part III of a three-part "Product Monograph" published when Beriplex® P/N was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Beriplex® P/N. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Beriplex® P/N 500 / Beriplex® P/N 1000, commonly known as Beriplex® P/N (Human Prothrombin Complex), is indicated for:

- Treatment of bleeding and prevention of bleeding prior, during, or following surgery in patients with 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.
- Beriplex® P/N can be used for the treatment of bleeding and perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin K dependent coagulation factors only if purified specific coagulation factor product is not available.

What it does:

In normal individuals, damage to blood vessels trigger a cascade of events that activate specific proteins present in their blood and which are responsible for the formation of a clot that ultimately stops the bleeding.

In patients treated with vitamin K antagonists (e.g. Warfarin, Coumadin, etc., or heparins), damage to blood vessels does not trigger the full cascade of events leading to the formation of blood clots.

Beriplex® P/N is used to treat or prevent bleeding in these patients by providing adequate amounts of the necessary missing or inhibited factors required for normal blood coagulation.

When it should not be used:

Beriplex® P/N should not be used if you are experiencing any of the following:

- Hypersensitivity to the active substance or to any of the excipients listed in section **Dosage Forms, Composition and Packaging**.
- Disseminated intravascular coagulation.
- Known history of heparin-induced thrombocytopenia.

What the medicinal ingredient is:

Beriplex® P/N is a lyophilised plasma protein preparation containing human plasma coagulation factors II, VII, IX and X, as well as protein C and protein S.

What the important non-medicinal ingredients are:

Human antithrombin III, heparin, human albumin, sodium chloride, sodium citrate, HCl or NaOH (in small amount for pH adjustment).

For a full listing of non-medicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Beriplex® P/N is available in single use vials of either 500 IU or 1000 IU. It comes in the form of a lyophilised powder (white or slightly coloured) to be reconstituted with the solvent provided in its carton prior to being administered by intravenous injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The use of prothrombin complex concentrates is associated with the risk of thrombosis. Cases of thrombosis have been observed in conjunction with treatment with Beriplex® P/N.

BEFORE you use Beriplex® P/N talk to your doctor or pharmacist if:

- You are on a controlled sodium diet.
- You have a history of coronary heart disease, myocardial infarction, liver disease, are at risk for thromboembolic phenomena or disseminated intravascular coagulation, or have simultaneous inhibitor deficiency.
- You are breastfeeding, pregnant or trying to become pregnant.
- Have recently undergone surgery.
- Are allergic to Beriplex® P/N, its ingredients or the components of its container.
- You are receiving vitamin K antagonists.
- You have a history of acquired or congenital deficiency of the vitamin K-dependent coagulation factors.
- You have a history of heparin-induced thrombocytopenia.

INTERACTIONS WITH THIS MEDICATION

Beriplex® P/N neutralises the effects of vitamin K antagonist treatments.

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.

PROPER USE OF THIS MEDICATION

Usual dose:

Every patient is different; your health professional will determine what dose of Beriplex® P/N is right for you and how often you should receive it.

Overdose:

Overdosage with prothrombin complex concentrates has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The risk of thromboembolic complications or disseminated intravascular coagulation due to overdosage is increased in patients at risk of these complications. Regular monitoring of the coagulation status will help avoid overdosage.

Reconstitution:

Beriplex® P/N should be reconstituted according to the instructions below. The reconstituted solution should be administered intravenously (not more than 3 IU/kg/min, max. 210 IU/min, approximately 8 ml/min).

Parenteral Products:

Bring the product and the solvent (diluent) to room temperature. Ensure that the product and solvent vial flip caps are removed and that the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial® package.

1. Open the Mix2Vial® package by peeling off the lid. Do **not** remove the Mix2Vial® from the blister package!

2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial® together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.

3. Carefully remove the blister package from the Mix2Vial® set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial® set.

4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial® set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.

5. With one hand grasp the product-side of the Mix2Vial® set and with the other hand grasp the solvent-side and unscrew counterclockwise the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial® adapter attached.

6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial®´s Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application:

8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial® adapter from the syringe by unscrewing counterclockwise.

Beriplex® P/N must not be mixed with other medicinal products, diluents or solvents.

The solution should be clear or slightly opalescent. After filtering/withdrawal, the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.

Because Beriplex® P/N contains no preservative; the reconstituted product should be used immediately to ensure its sterility. However, if it is not administered immediately, storage shall not exceed 3 hours at room temperature.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The administration of Beriplex® P/N is usually well tolerated. Replacement therapy may lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. The efficacy of the PCC treatment may be affected by the presence of these inhibitors.

A doctor should be called immediately if any of these reactions occurs:

- Tissue and abdomen swelling from excess salt and fluid retention, frothy urine (nephrotic syndrome);
- Thromboembolic episodes;
- Increase in body temperature;
- Hypersensitivity or allergic reactions (which may include angioedema, burning / stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, angina pectoris, tingling, vomiting or wheezing);
- Small blood clots or excessive bleeding due to depleted clotting factors (disseminated intravascular coagulation);
- Anaphylactic reactions including anaphylactic shock
- Development of antibodies to one or several factors of the prothrombin complex;
- Multiple purple pinpoint bruises, easy bruising, unusually heavy menstruation (could be caused by heparin-induced thrombocytopenia, type II).

Your doctor will decide whether it is appropriate or not to discontinue the treatment with Beriplex® P/N.

This is not a complete list of side effects. For any unexpected effects while taking Beriplex® P/N, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect*
- Call toll-free at 1-866-234-2345;
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Address Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

We recommend that CSL Behring Canada be copied when reporting suspected side effects, at the following address:
adversreporting@cslbehring.com

or be informed by pager
Pager Number: 1-613-783-1892

HOW TO STORE IT

Beriplex® P/N 500 and Beriplex® P/N 1000 can be stored either in the refrigerator or at room temperature (at +2°C to +25°C) for the period indicated by the expiration date printed on the carton and vial label. The shelf life of Beriplex® P/N is 36 months. **Avoid freezing**, which may damage the solvent container. Keep Beriplex® P/N in its box during storage.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www. cslbehring.ca

or by contacting the sponsor, CSL Behring Canada, Inc.

at: 1-613-783-1892.

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