Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Human Prothrombin Complex

Proprietary Product Name: Beriplex P/N

Sponsor: CSL Ltd Bioplasma Division

March 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision	15 January 2010
Active ingredient(s):	Human Prothrombin Complex
Product Name(s):	Beriplex P/N
Sponsor's Name and Address	CSL Limited Bioplasma Division 189-209 Camp Road Broadmeadows Vic 3047
Dose form(s):	Injection, reconstituted solution
Strength(s):	250 IU and 500 IU
Container(s):	Vial
Pack size(s):	Single pack contains one vial of product, one vial of Water for Injections and one Mix2Vial filter transfer device 20/20.
Approved Therapeutic use:	Treatment and perioperative prophylaxis of bleedings 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.
Route(s) of administration:	Intravenous
Dosage:	The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition.

Product Background

Normal human coagulation depends on a critical balance of a number of circulating plasma proteins in inactive forms, which are converted in a cascading fashion to active forms by limited proteolysis. The result of this "coagulation cascade" is the formation of thrombin, an enzyme converting fibrinogen to fibrin which finally, together with platelets and a linking protein, called factor XIII promotes the formation of a stable, cross-linked fibrin clot.

A number of coagulation factors are pivotal to the formation of thrombin (also called factor IIa), and therefore to haemostasis overall. The prothrombinase complex is produced by the cascading actions of factors VII, X and V. Several of these factors, namely factors VII, IX, X and factor II are synthesized in the liver in a process that depends on vitamin-K, whereas factor VIII and factor V are not. Collectively, factors II, VII, IX and X are known as the "vitamin-K-dependent" (VKD) coagulation factors. A number of other proteins also interact with the haemostatic system, including the regulating proteins Protein C and Protein S. The synthesis of these important regulatory proteins is not unique to the liver, but it also depends on a substrate of vitamin K.

Congenital deficiencies of any of the VKD factors listed above results in disturbance of the blood's normal ability to form clots. Haemophilia B, for example, is characterized by a deficiency of factor IX due to a gene mutation, and illustrates this point. Acquired deficiencies, however, are far more common.

Perhaps the most common cause of acquired deficiencies of the VKD clotting factors is iatrogenic and intentional. Warfarin (and drugs in its class) produces its therapeutic action by inhibiting the synthesis of all of the VKD clotting factors, including Proteins C and S. Warfarin is used extensively for this purpose, to inhibit thrombosis either primarily or as part of a prophylaxis strategy. Common modern indications include atrial fibrillation, prosthetic heart valves, deep vein thrombosis, and pulmonary embolism. Inhibition of thrombosis is not without risk, since normal haemostasis depends on it. Haemorrhage is significantly more likely under warfarin therapy, and treatment is generally aimed at maintaining a narrow range of the degree of anticoagulation. This is conventionally measured by the International Normalized Ratio (INR), a ratio of the prothrombin time (PT) compared to a normal control. In health, this is usually 0.8 – 1.2; depending on the therapeutic indication, under warfarin therapy the target INR is often 2.0 – 2.5. Unfortunately, for a variety of pharmacokinetic and pharmacodynamic reasons, warfarin is notorious for its nonlinear dose-response relationship and correct titration of dosing remains one of the most fraught problems in clinical practice.

Another common cause of acquired deficiency of the VKD factors is severe liver disease of any cause. Because all these factors are synthesized in the liver, hepatic failure usually results in a fall in the production of these factors and a resulting coagulopathy. This is usually measured by the INR, and is an important cause of morbidity and mortality in liver disease.

Less commonly, vitamin K deficiency states can cause a disturbance to normal haemostasis. Because bile is essential for vitamin K absorption, biliary obstruction can cause a deficiency. Antimicrobial therapy can disrupt gut flora to the point where vitamin K absorption is impaired.

Regardless of the root cause, deficiency of any or all of the VKD coagulation factors exposes the patient to increased risk of adverse haemorrhagic events. This risk probably rises exponentially with increasing INR. There clearly exists a range of circumstances in which rapid reversal of this deficiency of VKD factors is required. Examples include the perioperative period, where patients with factor deficiency need urgent surgery or where the time spent "un-anticoagulated" must be minimized as part of a risk-management strategy. Further, patients with active haemorrhage may require urgent reversal of their factor deficiency.

In Australia in 2009, there exist three options for the treatment or prevention of bleeding in patients deficient in the VKD coagulation factors. Fresh frozen plasma (FFP) is the fluid portion of human blood that has been centrifuged, separated and frozen within six hours of collection. It contains all elements of the normal coagulation, fibrinolytic and complement systems, including the VKD factors II, VII, IX, X, protein C and protein S. While this may seem the ideal therapy for patients deficient in VKD factors, there are a number of problems associated with the urgent and emergent use of FFP. These include the need for isoagglutinin ("blood group") compatibility, the risk of blood-borne virus transmission, protein and anaphylatoxin load, fluid overload, and electrolyte disturbance. A second option for the treatment of VKD factor deficiency is vitamin K itself, either orally or intravenously. Although vitamin K is efficacious, its maximal effect is not noted until around 24 hours after administration even when given intravenously, and as such it cannot be considered acceptable monotherapy when a rapid response is needed. The third option is the use of a prothrombin complex concentrate which contains the VKD factors in concentrated form.

Two prothrombin complex concentrates are currently registered in Australia, although only one is readily available. Prothrombinex-VF (CSL Ltd) was marketing prior to 1991 and not evaluated by the TGA prior to marketing. Although it contains similar activities of factors II, IX and X as Beriplex P/N, it contains minimal amounts of factor VII, protein C and protein S. It is used widely, and for the same indications being sought in this application, although the major local guidelines recommend the concomitant use of FFP in order to provide (in particular) factor VII substrate. Pronativ (Octapharma Australia Pty Ltd) was registered in September 2007, and is similar to Beriplex P/N in active ingredients and proposed indication. It is understood that Pronativ is not currently being marketed in Australia.

The sponsor submitted an application to register a new prescription medicine, Beriplex P/N, in Australia. The product is intended to be registered as a contingency product only. Beriplex P/N is a plasma-derived preparation of purified human prothrombin complex.

The proposed indication for both strengths of the drug is twofold. It is proposed for the treatment and perioperative prophylaxis of bleedings 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. It is also proposed for the treatment and perioperative prophylaxis of bleedings in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor products are not available.

The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition. The amount and 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. The dose will depend on the International Normalised Ratio (INR) before treatment and the targeted INR.

Regulatory Status

Beriplex P/N has been approved for use in a number of other countries. In Argentina and Brazil, it has been registered since 2001. It was approved in Taiwan in 1999, and in Malaysia in 2004. A number of European countries have approved the product, including Germany in 1996, and Great Britain, Spain and Switzerland in 2008. The drug's product information in the EU countries contains the same proposed indication being sought in this application.

The submission states that no application has been made to register the drug in the United States or Canada.

The sponsor has provided assurance that no country has suspended registration status and that voluntary withdrawals of applications have occurred for business/commercial reasons only (not for safety or efficacy reasons).

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Following reconstitution, the solution of both presentations contains 20 – 31 IU Factor IX per mL (with a nominal target value of 25 IU Factor IX per mL) (Table 1). The concentration of other coagulation factors depends on the starting material (human plasma) and the

fractionation process. One IU of a coagulation factor activity is equivalent to the quantity in one mL of normal human plasma.

Table 1: Composition of the drug substance

Name of the ingredients	Content after reconstitution (IU/mL)	Beriplex P/N 250 content per vial (IU)	Beriplex P/N 500 content per vial (IU)
Active Ingredients			
Human coagulation factor II	20 – 48	200 – 480	400 – 960
Human coagulation factor VII	10 – 25	100 – 250	200 – 500
Human coagulation factor IX	20 – 31	200 – 310	400 – 620
Human coagulation factor X	22 – 60	220 – 600	440 – 1200
Other active ingredients			
Protein C	15 – 45	150 – 450	300 – 900
Protein S	12 – 38	120 – 380	240 – 760

The total protein content is 6 – 14 mg/mL of reconstituted solution.

The drug substance is manufactured by CSL Behring in Marburg, Germany and another six sites (Switzerland (2 sites), the USA (2), Germany and Ireland) are involved in the testing of the substance. All sites have GMP clearance. The manufacturing process of the drug substance involves 10 steps as follows:

- Fractionation of plasma to cryo-depleted plasma
- Adsorption/isolation of prothrombin complex
- Stabilisation
- Virus inactivation (pasteurisation)
- Removal of high MW proteins
- Adsorption/isolation of prothrombin complex
- Ultracentrifugation
- Stabilisation
- Virus filtration
- Ultrafiltration

The proposed in-process control specifications control the potency of selected active and excipient ingredients of the drug substance relevant to the dose form and its intended clinical use. Appropriate validation data have been submitted in support of the test procedures.

The proposed release specifications for the Beriplex P/N and Water for Injections are satisfactory. The current Ph. Eur. describes a two-stage chromogenic assay for testing the activity of coagulation factors II, VII, IX and X. At CSL Behring a one-stage clotting assay is used for release testing which has been appropriately validated.

The manufacturing process validation included an investigation of impurity profile of the product during the production process and in the final product. Besides degradation products of thrombin and albumin, a number of human plasma proteins “were identified in small amounts”. The sponsor was asked to provide justification as to why these proteins would not represent a safety risk to patients who receive Beriplex P/N. The response was referred to the Delegate and the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation

Committee (ADEC) for comment. The Delegate and the PSC considered the response acceptable.

The sponsor has stated that the plasma used as the source of the active ingredients is collected, tested, stored and transported in accordance with the information given in the currently valid CSL Behring plasma master file. The TGA has evaluated the 2008 annual update of the CSL Behring Plasma Master File containing epidemiology data for the 2007 calendar year. The update was found to be acceptable.

Drug Product

After ultrafiltration the Prothrombin Complex Ultraconcentrate is immediately processed (without holding) to make the drug product according to the following steps:

- Blending and final adjustment
- Sterilising filtration
- Filling
- Lyophilisation
- Packaging
- Batch release

In addition to Prothrombin Complex, the drug product contains the excipients heparin sodium, human antithrombin III, human albumin, sodium chloride, sodium citrate, HCl and NaOH (all Ph Eur). The diluent (Sterilised Water for Injections) is supplied in 10 mL and 20 mL volumes for the 250 IU and 500 IU dosage strengths, respectively.

Sterility

Sterility aspects of the product have been reviewed. The assessment only covers the lyophilised product and diluent, not the Mix2Vial transfer device supplied as part of the pack. The Mix2Vial will be assessed as part of the medical device application for a procedure pack. Several labelling issues were raised – these have been resolved. Further information regarding the integrity testing of filter elements, bioburden testing, media fill validations, the terminal steam sterilisation process for the diluent vials, and compliance with the Ph.Eur. sterility test was requested and supplied. The company was asked to lower the pre-sterilisation bioburden limit. The sponsor committed to such lowering. There are no outstanding issues with regards to sterility safety

Container safety

The injection vials and stoppers (250 IU, 500 IU and Water for Injections) and crimp caps were assessed. There are no outstanding issues with regards to container safety.

Endotoxin/pyrogen safety

Endotoxin safety aspects of the product have been reviewed and found to be acceptable. Therefore, there are no outstanding issues with regard to endotoxin safety.

Pre-registration testing

Beriplex P/N is intended to be registered as a contingency product for the Australian Market. In view of this information, the Biochemistry Section of the TGA's Office of Laboratories and Scientific Services has advised that pre-registration testing is not warranted. As a condition of registration the sponsor will be required to submit the first five batches of Beriplex P/N for testing and approval before release of each for sale, and this is considered appropriate given its intended use as a contingency product.

Viral/Prion safety

The viral safety aspects of the active ingredient and relevant excipients (heparin, anti-thrombin III, human albumin) have been reviewed. It was concluded that the viral safety of Beriplex P/N indicates that there is a good margin of safety for the enveloped viruses. For non-enveloped viruses, the margin of safety for HAV and B19 is much lower, however, due to the presence of antibodies, neutralisation of HAV and B19 can occur in the pooled plasma.

Bioavailability

Bioavailability data are not required for this product because the route of administration of Beriplex P/N is intravenous.

Storage/shelf-life

Beriplex P/N

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability studies were not performed. However photostability is assured by the packaging and directions to the consumer that the vial must be kept in the outer container in order to protect the product from light.

The proposed shelf life is 36 months when stored at +2 to 25˚C/ 60% RH. The results of three studies were provided in support of the stability. The first two studies were undertaken over a period of 42 months and the results support the proposed shelf life.

The third study was undertaken using the 500 IU dosage strength of Beriplex P/N formulated with Alburex 25 (25% human albumin). The final concentration of albumin in Beriplex P/N stabilised with Alburex is the same as that of Beriplex P/N stabilised with Human Albumin 20% Behring. The stability study for Beriplex P/N stabilised with Alburex 25 is ongoing. Eighteen months of data was supplied to the TGA in April 2009. The results were within the pre-defined specification limits. The sponsor provided assurance that the TGA would be notified of any trends or out of specification results from this study as the results become known, and that the TGA would be notified of the overall study results upon completion of the study.

In-use stability data were generated in parallel with the closed shelf life data. The shelf-life that was initially proposed for the reconstituted product was 8 hours at +2˚C to 25˚C. The sponsor has since reduced the proposed shelf-life for the reconstituted product to 6 hours at +2˚C to 25˚C in order to comply with Appendix 12 of the ARGPM. Based on the data provided, a shelf-life of 6 hours at +2 to 25˚C after reconstitution is considered appropriate provided that this claim is further substantiated.

Water for Injections

The proposed shelf life is 60 months when stored at +2 to 25˚C/ 60% RH. The information provided supports the proposed shelf life.

Quality Summary and Conclusions

Quality information concerning Beriplex P/N was tabled at the 127th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC). At the time of the meeting, two issues remained outstanding. These issues have since been resolved.

There were no objections to the registration of the products on quality grounds.

III. Nonclinical Findings

Introduction

Due to the nature of the product (human origin), standard pharmacokinetic and toxicity studies with the proposed product in heterologous experimental species are not considered appropriate or necessary. Repeat-dose toxicity testing and embryofetal studies are impractical due to the induction of, and interferences by, antibodies. Nonetheless, several safety pharmacology, single-dose toxicity, local tolerance and pharmacodynamic studies were submitted. The studies used two preparations of the prothrombin complex, Beriplex HS and Beriplex P/N, which differ by the inclusion of a nanofiltration step in the latter preparation. There was no apparent difference in pharmacology or toxicity between the two preparations and for the purposes of this assessment, the 2 formulations were considered synonymous.

Pharmacology

Primary pharmacodynamics

Given the extensive use of coagulation factors for the treatment of haemophilia A, haemophilia B, congenital deficiencies in Factor IX, II or X, as well as acquired vitamin K deficiencies only a small number of pharmacodynamic studies were performed. According to the nature of the product, pharmacodynamic testing addressed its procoagulatory activity. The pharmacodynamic effects of Beriplex HS and Beriplex P/N were investigated *in vivo* in a stasis thrombogenicity model in rabbits. Beriplex P/N was evaluated in a coumarin reversal model in rats and using a modified thromboelastography (TEG) method in pigs.

Consistent with the expected pharmacology, Beriplex P/N (50 IU/kg) normalised coagulation parameters and prevented excessive bleeding from a coumarin overdose (vitamin K deficiency) in rats. Decreased coagulation time and clot formation time with no effect on maximal clot firmness were observed in pigs at 36.8 IU/kg. At a cumulative dose of 90 IU/kg in dogs, effects associated with the pharmacology were observed: decreased Quick percentages and TEG times, associated with the active ingredients. Decreased platelets were observed in dogs treated with ≥20 IU/kg which is likely associated with heterologous plasma components. Some variability in coagulation parameters and TEG times were observed in dogs, which can be attributed to the heparin and/or antithrombin component(s) in the formulation. Taken together, these results suggest the potential of Beriplex P/N for use as substitution therapy during vitamin K deficiency disorders at the proposed clinical dose of 100 IU/kg.

Safety Pharmacology

Five studies in conscious and anaesthetised dogs addressed the safety pharmacological aspects of Beriplex HS and Beriplex P/N. All studies examined potential secondary pharmacological effects of IV administration of Beriplex HS or Beriplex P/N on the cardiovascular system and respiration, as well as haematological parameters in beagle dogs.

Increased systolic and diastolic blood pressure, reduced heart rate and increased cardiac output were consistently observed. All of these could be related to the large injection volumes. Otherwise, Beriplex P/N was well tolerated regarding cardiovascular and respiratory parameters up to a cumulative dose of 350 IU/kg, which is greater than 3-fold the maximum recommended human dose (MRHD).

Pharmacokinetics

No pharmacokinetic studies were provided.

Toxicology

General toxicity

Three acute toxicity studies in rodents were submitted. Acute intravenous (IV) toxicity studies with Beriplex HS were performed in mice and rats and with Beriplex P/N in rats (Table 2). All studies were GLP-compliant.

Table 2. Summary of single-dose toxicity studies with Beriplex HS and Beriplex P/N

Species & strain	Formulation	Dose (IU/kg)
Mouse (NMRI)	Beriplex HS[a]	0, 20, 60, 200
Rat (Wistar)	Beriplex HS[a]	0, 20, 50, 100
	Beriplex P/N[b]	0, 50, 100, 500

[a]Performed with a 14 day observation period; [b] with a 6 day observation period.

The maximum non-lethal dose and No Observable Adverse Effect Level (NOAEL) for mice and rats was 60 and 100 IU/kg, respectively; approximately the MRHD. At 5 times the proposed clinical dose (500 IU/kg), reduced red cell parameters, haematopoiesis in the liver, increased severity of tubular basophilia in the kidneys, atrophy of the thymus, prostate and seminal vesicles were observed in rats. All of these could be associated with a thromboembolic event and disseminated intravascular coagulation. This toxicity data, combined with an increase in thrombogenicity in rabbits at 200 IU/kg (2-fold the MRHD) but not 20 IU/kg, suggest there is a potential for thrombogenicity and thromboembolism at high doses of Beriplex P/N.

A comparative thrombogenicity study of Beriplex P/N with existing products was not performed and therefore it is inconclusive as to whether Beriplex P/N has a greater potential for thromboembolic adverse effects than similar products.

Local tolerance

Two studies were submitted in which the two different formulations, Beriplex HS and Beriplex P/N, were examined for local tolerance by the intended clinical route (IV) as well as Beriplex HS in the paravenous (PV) and intra-arterial (IA) administration in rabbits.

A local tolerance study after intravenous dosing (125 IU) with Beriplex P/N did not reveal any local intolerance. Beriplex HS was regarded as moderately tolerable after 100 IU (IV or intra-arterial) or 2 IU (paravenous) injections to rabbits. Immediate but reversible perivascular redness with histopathological findings of inflammatory oedema was observed after injection in rabbits. At a higher dose (500 IU/kg) to rats, mixed cell infiltration and myodegeneration at the injection site were observed. These effects are likely to be immune-reaction mediated as a result of the administration of heterologous proteins. Immune and/or anaphylactic reactions may occur in humans, but the frequency with which this happens will need to be ascertained by clinical data.

Nonclinical Summary and Conclusions

Beriplex P/N (50 IU/kg) normalised coagulation parameters and prevented excessive bleeding from a coumarin-overdose (vitamin K deficiency) in rats. Additional data suggested effects on the coagulation pathway in pigs (36.8 IU/kg) and dogs (cumulative dose of 90 IU/kg), supporting the potential of Beriplex P/N as substitution therapy of vitamin K deficiency disorders at the proposed clinical dose.

Three acute toxicity studies in rodents were submitted. The maximum non-lethal dose and NOAEL for mice and rats were 60 and 100 IU/kg, respectively; approximately the maximum recommended human dose (MRHD), based on Factor IX activity.

Evidence of thromboembolism and thrombogenicity was observed at 500 IU/kg in rats and 200 IU/kg in rabbits, about 5- and 2-fold the proposed MRHD. These effects occur at similar doses to currently registered plasma-derived coagulation factor mixtures.

Beriplex P/N (125 IU) did not reveal any local intolerance. Consistent with other human plasma-derived coagulation factor products, the major toxicological concerns with Beriplex P/N were thrombogenicity and immune reaction/anaphylactic responses.

There are no objections on nonclinical grounds to the registration of Beriplex P/N for the proposed indication. However, due to the nature of the product (human origin), limited nonclinical data were submitted and safety and efficacy will need to be more comprehensively addressed by clinical data.

IV. Clinical Findings

Introduction

The application to register Beriplex P/N in Australia was presented in CTD format on a single DVD. There were 44 volumes of data available for evaluation, including complete study reports for six clinical trials.

One Phase I trial examined the drug's pharmacokinetics as a primary endpoint (Study BE1116-1001). The Phase III trial (Study BE1116-3001), which may be considered pivotal to the application, also reported pharmacokinetic data as a secondary endpoint.

Efficacy data was generated from one Phase III trial (Study BE1116-3001) and one Phase II trial (Study BE1116/7D-201KO). Two investigator-sponsored studies were also included (Evans et al., 2001; Preston et al., 2002) as supportive studies.[1,2] The data for the latter two studies are derived from the published literature. Some supporting efficacy data was provided from a very small Phase II trial (Study BE1116/7D-202KO) in which only two patients were enrolled. Clinical efficacy endpoints varied among the studies, and included conventional measures such as the INR (discussed in Section 1 above) and less-familiar indices of coagulation such as the Quick's Value (discussed in Pharmacodynamics below). In addition, many of the studies report the "*in vivo* recovery" (IVR) of each measured factor[3].

All six of the submitted studies reported safety data. Relevant ethics approvals were explicitly reported as granted for all but the study by Evans et al., 2001. Company sponsored studies BE1116-3001, BE1116-1001, BE1116/7D-201KO and BE1116/7D-202KO were conducted in accordance with GCP guidelines – this is not stated explicitly in the published trials by Evans et al., 2001 and by Preston et al., 2002. No long-term safety data was presented, and all but seven of the 142 patients involved in the clinical development programme received only a single dose of the study drug.

Pharmacokinetics

The Phase I trial BE1116-1001 reported pharmacokinetic data as a primary endpoint. In addition, the pivotal Phase III trial BE1116-3001 reported pharmacokinetic data secondarily.

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[1] Evans G, Luddington R, Baglin T. Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding. Br J Haematol 2001; 115: 998-1001.

[2] 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: 619-624.

[3] This is the actual rise of measured factor (in percent) divided by the theoretical rise of measured factor (in percent). In turn, the theoretical rise is the dose of factor (in IU) divided by plasma volume (in mL, generally 41 × body weight in kg).

The formulation of Beriplex used in the submitted clinical studies was the same as the formulation subject to this application, namely Beriplex P/N. This replaced an earlier-developed product (Beriplex HS) in 1996, and differs from it only in the addition of a nanofiltration process as a secondary viral inactivation step.

The formulation used in the clinical studies was identical to that being proposed for marketing, and was supplied in two presentations: Beriplex P/N 250 and Beriplex P/N 500. Both presentations include a vial of lyophilized drug product in sterile glass, a vial of water for injections (WFI), and a transfer device for the transmission of diluent into the product vial. After reconstitution both presentations contain between 20 IU/mL and 31 IU/mL of factor IX (the lead factor for potency). The nominal target concentration of factor IX in the reconstituted substance is 25 IU/mL.

Study BE1116-1001

This trial was a Phase I, single-centre, prospective uncontrolled open-label study of a single IV dose of 50 IU/kg of Beriplex in 15 healthy subjects. After a single dose of the study drug, determinations of pharmacokinetic variables were made before the infusion, and at intervals of 5, 10, 15 and 30 minutes, and 1, 2, 3, 4½, 6, 9, 12, 15, 18, 24, 32, 48, 72, 96 and 144 hours after the end of the infusion. These time intervals were chosen both to cover a reasonable window of observation, and were based on known plasma half-lives of the active ingredients as reported in the literature. Individual factor activity determinations were made from citrated blood using a chromogenic substrate method, a manufacturer-specific Coagulation Timer and reagents; these were validated to appropriate standards.

The investigators offered an adequate rationale for the use of healthy subjects. Patients with acquired VKD factor deficiency (such as through oral anticoagulation) could not safely have their coagulation normalized. Patients with liver disease were also inappropriate given the heterogeneity of their illness. Patients with congenital single or combined VKD factor deficiency are rare enough that recruiting a population would not be feasible.

A population size of 15 was designed to exceed the specifications of the active CPMP guidance note for pharmacokinetic studies of plasma-derived factor VIII and factor IX products which recommends at least 12 subjects for pharmacokinetic studies.[4] All subjects received 50 IU/kg of study drug. The drug was given by infusion over a median of 19 minutes.

The pharmacokinetic parameters reported included incremental *in vivo* recovery (IVR), half-life, area under the concentration-time curve, clearance, mean residence time (MRT), and steady-state volume of distribution. These were reported for each of the active ingredients: factor II, factor VII, factor IX, factor X, protein C and protein S. This data is presented in Table 3.

Steady-state volumes of distribution suggested that factors II, IX, protein C and protein S were distributed beyond the plasma compartment, while factors VII and X remained within it. Factors VII and IX had a relatively rapid clearance and short half-life (median half-lives of 4 and 17 hours respectively) compared to the other active ingredients.

[4] Committee for Proprietary Medicinal Products. Note for guidance on the clinical investigation of human plasma derived factor VIII and IX products. *TGA*. [Online] 19 October 2000. [Cited: 15 May 2009.] http://www.tga.gov.au/docs/pdf/euguide/bpwg/019895en.pdf.

Table 3 - Pharmacokinetic parameters (BE1116-1001)

	Parameter	Median	Range	Mean	SD*
Factor IX	Initial half-life (h) (N=12)	7.0	2.9 – 14.2	7.0	3.0
(N = 15)	Terminal half-life (h)§	16.7	9.5 – 127.1	42.4	41.6
	C_{max} (%)	170	123 – 213	172.3	28.8
	Dose adjusted AUC (kgxh/dL)*	27.5	14.7 – 76.4	34.2	18.5
	Clearance (mL/(kg x h))	3.6	1.3 – 6.8	3.7	1.6
	MRT (h)#	21.6	13.3 – 161.2	47.3	49.5
	V_{ss} (mL/kg)**	92.4	56.5 – 210.9	114.3	54.6
Factor II	Initial half-life (h) (N=14)	6.2	2.3 – 11.4	6.2	2.4
(N = 15)	Terminal half-life (h)§	59.7	25.0 – 135.3	60.4	25.5
	C_{max} (%)	238	195 – 265	235.7	21.5
	Dose adjusted AUC (kgxh/dL)*	102.8	59.9 – 211.3	113.7	36.3
	Clearance (mL/(kg x h))	1.0	0.5 – 1.7	1.0	0.3
	MRT (h)#	81.7	36.1 – 185.8	82.0	34.2
	V_{ss} (mL/kg)**	71.0	47.5 – 101.0	71.4	13.7
Factor VII	Half-life (h)§	4.2	2.1 – 9.2	5.0	1.9
(N = 15)	C_{max} (%)	170	118 – 203	165	22.5
	Dose adjusted AUC (kgxh/dL)*	14.2	5.7 – 34.7	17.1	8.3
	Clearance (mL/(kg x h))	7.1	2.9 – 17.6	7.4	4.1
	MRT (h)#	6.1	3.0 – 13.3	7.2	2.7
	V_{ss} (mL/kg)**	41.8	29.2 – 68.8	45.0	10.7
Factor X	Half-life (h)§	30.7	16.9 – 43.8	31.8	8.7
(N = 15)	C_{max} (%)	263	228 – 380	273.4	39.1
	Dose adjusted AUC (kgxh/dL)*	80.2	57.1 – 117.0	82.5	20.7
	Clearance (mL/(kg x h))	1.25	0.9 – 1.8	1.3	0.3
	MRT (h)#	44.3	24.3 – 63.2	45.9	12.6
	V_{ss} (mL/kg)**	56.1	39.3 – 65.2	55.5	6.7
Protein C	Initial half-life (h) (N=12)	6.7	4.7 – 8.7	6.8	1.0
(N = 15)	Terminal half-life (h)§	47.2	9.3 – 121.7	49.6	32.7
	C_{max} (%)	278	225 – 320	273.8	30.8
	Dose adjusted AUC (kgxh/dL)*	91.0	30.6 – 180.5	93.2	45.2
	Clearance (mL/(kg x h))	1.1	0.6 – 3.3	1.5	0.9
	MRT (h)#	57.0	13.4 – 161.4	62.4	42.1
	V_{ss} (mL/kg)**	62.9	43.9 – 109.3	62.2	17.4
Protein S	Initial half-life (h)	4.7	0.9 – 7.0	4.2	1.8
(N = 15)	Terminal half-life (h)§	49.1	33.1 – 83.3	50.4	13.4
	C_{max} (%)	162	138 – 218	170.2	25.9
	Dose adjusted AUC (kgxh/dL)*	90.0	54.7 – 144.1	89.9	22.5
	Clearance (mL/(kg x h))	1.1	0.7 – 1.8	1.2	0.3
	MRT (h)#	69.2	45.3 – 113.5	70.3	18.3
	V_{ss} (mL/kg)**	76.6	61.9 – 105.0	78.8	11.6

Study BE1116-3001

This trial was a Phase III, multi-centre, prospective uncontrolled open-label study of the ability of a single IV infusion of Beriplex to reverse the effects of oral anticoagulation in 43 patients, as measured by a fall in INR values. Because it was primarily a trial of efficacy and safety, its design and characteristics are discussed in more detail under *Efficacy* below. However, as a secondary endpoint it also reported pharmacokinetic data, in the form of measured plasma levels of factors II, VII, IX and X, as well as protein C. It is therefore also mentioned here. Plasma levels were determined at baseline, and at 30 minutes, and 1, 3, 6, 12, 24 and 48 hours after the end of the infusion. The assay method was as for the study BE1116-1001. The study drug was given as a single IV infusion, but in a dose that varied according to the baseline INR: 25 IU/kg for an INR between 2 and 3.9, 35 IU/kg for an INR between 4 and 6, and 50 IU/kg for an INR greater than 6.

44 subjects were enrolled (22 males, 22 females) but one withdrew before treatment. Of the remaining 43 subjects, 26 were assigned to the 25 IU/kg treatment group, 7 to the 35 IU/kg treatment group and 10 to the 50 IU/kg treatment group. Adults over the age of 18 who had a baseline INR greater than 2 as a result of oral anticoagulation therapy were included, if they required urgent reversal for the purposes of emergency surgery, an invasive diagnostic procedure, or the treatment of acute haemorrhage. The median dose administered was 2320 IU, 3000 IU and 4120 IU to the 25 IU/kg, 35 IU/kg and 50 IU/kg groups respectively.

Pharmacokinetic parameters measured included plasma levels of factors II, VII, IX and X, and proteins C and S (Table 4). These data support the findings of the earlier Phase I study in that a single dose of Beriplex can be expected to normalize plasma levels of the relevant coagulation factors, in this case in a population with acquired VKD factor deficiency. It is worth noting, however, the variability of maximal median after baseline. In particular, for factor VII (which the Phase I trial demonstrated had the shortest half-life) the maximal median recovery after baseline was only 55% in the 50 IU/kg group, and 69% in the 35 IU/kg group. It may be that those patients with a very high INR (greater than 6) would require particularly careful monitoring; this study suggests that this group of patients is likely to experience relatively poor recovery of factor VII (also the factor with the shortest half-life).

Table 4 - Median levels of component factors by dose group (BE1116-3001)

IMP component	Dose / baseline INR group	Median baseline level, %; (Range, %)	Maximal median after baseline (%)*	Range of all values after baseline (%)+
FIX	25 IU/kg (INR 2 – <4)	43 (26 – 113)	104	24 – 183
	35 IU/kg (INR 4 – 6)	23 (12 – 40)	77.5	25 – 160
	50 IU/kg (INR > 6)	14.5 (10 – 44)	87.5	36 – 143
FII	25 IU/kg (INR 2 – <4)	26 (14 – 60)	90	46 – 147
	35 IU/kg (INR 4 – 6)	12 (4 – 13)	100	30 – 145
	50 IU/kg (INR > 6)	4 (4 – 24)	108	32 – 155
FVII	25 IU/kg (INR 2 – <4)	23 (10 – 73)	83	18 – 146
	35 IU/kg (INR 4 – 6)	16 (4 – 46)	69	8 – 114
	50 IU/kg (INR > 6)	4 (4 – 26)	55.5	4 – 100
FX	25 IU/kg (INR 2 – <4)	13 (4 – 50)	93.5	33 – 190
	35 IU/kg (INR 4 – 6)	4 (4 – 9)	117	32 – 185
	50 IU/kg (INR > 6)	4 (4 – 24)	142	40 – 223
Protein C	25 IU/kg (INR 2 – <4)	43 (27 – 100)	110	54 – 180
	35 IU/kg (INR 4 – 6)	37 (14 – 62)	133	40 – 171
	50 IU/kg (INR > 6)	24.5 (9 – 54)	132	41 – 202
Protein S	25 IU/kg (INR 2 - <4)	36.9 (22 – 73)	78.4	36 – 108
	35 IU/kg (INR 4 – 6)	17.3 (8 – 38)	60.2	15 – 101
	50 IU/kg (INR > 6)	21.5 (16 – 28)	94.8	27 – 133

Adsorption, Distribution, Metabolism and Excretion

No studies specifically addressing the absorption, distribution, metabolism or excretion of Beriplex (either in animal models or a human population) were submitted with this

application. However, the pharmacokinetic study BE1116-1001 allows some comment to be made here.

Absorption

As a proposed IV infusion, the study drug has 100% bioavailability. Given that no route other than the IV route was considered (or would be appropriate for the indications sought in the submission) no studies of absorption were required.

Distribution

The volume of distribution varied across the individual factors in the preparation. V_{ss} (mean ± standard deviation) was 71.4 ± 13.7mL/kg for factor II, 45.0 ± 10.7mL/kg for factor VII, 114.3 ± 54.6mL/kg for factor IX, 55.5 ± 6.7mL/kg for factor X, 62.2 ± 17.4mL/kg for protein C and 78.8 ± 11.6mL/kg for protein S. This implies that the distribution of factors VII and X remained within plasma, whereas the other factors were distributed slightly beyond it.

Metabolism

None of the submitted studies evaluated the metabolism of Beriplex. It is expected that the factors in the preparation would be cleared predominantly by catabolism.

The terminal plasma half-lives (mean ± standard deviation) were 60.4 ± 25.5hr for factor II, 5.0 ± 1.9hr for factor VII, 42 ± 41.6hr for factor IX, 31.8 ± 8.7hr for factor X, 49.6 ± 32.7hr for protein C and 50.4 ± 13.4hr for protein S. Other than for factor IX (where it will be noted there was very significant variability) these half-lives are consistent with those previously published.

Excretion

Elimination of factors VII and IX was reflected by a more rapid clearance and shorter half-life. Cl (mean ± standard deviation) was 1.0 ± 0.3ml/kg·hr for factor II, 7.4 ± 4.1ml/kg·hr for factor VII, 3.7 ± 1.6ml/kg·hr for factor IX, 1.3 ± 0.3ml/kg·hr for factor X, 1.5 ± 0.9ml/kg·hr for protein C and 1.2 ± 0.3ml/kg·hr for protein S.

Drug Interactions

No clinical studies of the pharmacokinetics of drug interactions with Beriplex were performed.

Pharmacodynamics

None of the studies from the clinical data section of the submission reported pharmacodynamic data.

Pharmacodynamics of Prothrombin Complex Concentrates in Acquired VKD Factor Deficiency

As outlined in Section 1 above, the most common VKD factor deficiencies are acquired, and often iatrogenic (as a result of therapy with oral anticoagulants such as warfarin). In this case, activity of all the VKD factors is likely to be depressed. As such, the rationale for replacing all factors to "normal" levels is clear.

Pharmacodynamic modelling of the entire coagulation cascade for the study of Beriplex therapy of acquired VKD factor deficiency would be unnecessarily complex. All studies in the clinical dossier reporting efficacy use variants of the prothrombin time as a surrogate measure of the "degree" of acquired VKD factor deficiency and of the pharmacodynamics describing the actions of Beriplex on the body.

The prothrombin time (PT) measures the time taken for a given sample of plasma to clot after the addition of tissue factor. It is a measure of the quality of the so-called "extrinsic pathway" as well as the "common pathway" of the coagulation cascade. The extrinsic and common pathways depend on factor X, factor II and factor VII activity. Of these, it is likely that factor

VII is the most important since it has the shortest half-life, at 3 – 6 hours. Clinical practice accepts the use of PT (and particularly of its derived measure, the INR) as a reasonable surrogate marker of the inhibition of the factors involved in acquired VKD deficiency. Although the degree of deficiency of the individual factors probably varies from case to case, it is not common practice to measure the specific activities of factors II, VII, IX or X. In the case of oral anticoagulation with warfarin, the INR is used as a surrogate marker in the titration of dose to therapeutic effect.

Two of the clinical studies use as a pharmacodynamic efficacy measure the "Quick's Value". Armand Quick discovered the PT in 1935 and developed the eponymous value – a percentage – as a function of the reciprocal of the PT. As such, it too is a reasonable measure of the activity of the extrinsic and common pathways as a whole, and has a direct relationship with the INR. The Quick's Value was once the measure used to titrate oral anticoagulation, but was replaced in the 1980s with the INR to deal with inter-rater assay differences associated with the purity of tissue factor concentrate used to measure the PT. Although modern clinicians have little familiarity with the Quick's Value, when derived from modern assays (as it was in the clinical trials in the dossier) it is also considered an acceptable global measure of VKD factor activity.

Pharmacodynamics of Prothrombin Complex Concentrates in Congenital VKD Factor Deficiency

Congenital deficiency of any of the vitamin K-dependent (VKD) coagulation factors is rare, sufficiently so that detailed study of cohorts of these patients is not feasible.

Inherited factor II deficiency, first described by Quick in 1947, is a very rare autosomal recessive disorder manifesting as either a decrease in the overall synthesis of prothrombin or the synthesis of dysfunctional prothrombin. Homozygous individuals are usually asymptomatic but have functional prothrombin levels between 2% and 25% of normal. Heterozygous individuals are almost always asymptomatic and have levels of greater than 50%.

Congenital factor X deficiency is one of the medicine's most rare coagulopathies. Telfer in 1956 and Hougie in 1957 independently described this in two individuals with bleeding tendencies. Similarly, heterozygous individuals usually remain asymptomatic despite demonstrably reduced serum activities of factor X, while homozygous individuals may exhibit easy bruising, haematuria, menorrhagia, recurrent epistaxis or other manifestations of a bleeding tendency.

Inherited factor VII deficiency has an incidence of around one case per 500,000 and seems more common in countries where consanguineous marriage is more common. Of all the VKD factor deficiencies, this deficiency appears to have the poorest correlation between genotype and phenotype.

Perhaps the least rare and best understood of the VKD factor deficiencies is that of factor IX, also known as Haemophilia B (and formerly as Christmas' Disease). This X-linked disorder (transmitted by females and usually manifested in males) has an incidence of around one case per 30,000 male births. In this case, the severity of clinical manifestations correlates better with serum functional factor levels; in moderate disease (factor levels 2-5%), haemorrhage is likely with minor trauma or surgery, and spontaneous haemarthrosis occurs occasionally.

There is general agreement that the optimal treatment for the congenital VKD factor deficiencies is targeted replacement of the specific factor that is deficient, ideally with recombinant specific factor, rather than with prothrombin complex concentrates (PCCs). Recombinant factors, such as Wyeth's Benefix™ in Haemophilia B, have largely replaced

the historical use of the PCCs. This approach offers a number of advantages: PCCs have a relatively poorly defined mode of action, a rather unpredictable haemostatic response possibly contributing to thrombosis, and a small but real possibility of blood-borne viral transmission compared to recombinant technology.

Various treatment algorithms have been developed to manage the appropriate treatment with recombinant specific factors. These usually use a decision matrix including the nature of the haemorrhage (minor, moderate, major) and the patient's measured factor activity; the schedule even with this directed treatment is complex, based on minimal data, and still somewhat empirical.

Concerns exist about the use of PCCs for this indication. The literature includes numerous case reports of patients with Haemophilia B treated with PCCs developing thrombotic complications including disseminated intravascular coagulation and acute myocardial infarction. It is thought that activation of the clotting factors and the accumulation to high levels of factors other than the congenitally deficient factor is the mechanism responsible.

Efficacy

The efficacy of Beriplex was investigated in a population of 127 patients (72 men and 55 women) spread across the five submitted studies of efficacy. The pivotal study BE1116-3001 examined efficacy in 43 patients receiving oral anticoagulation; study BE1116/7D-201KO involved 8 patients receiving oral anticoagulation and 22 patients with severe liver disease; the study by Preston *et al.* (2002) and the study by Evans *et al.* (2001) involved 42 and 10 patients receiving oral anticoagulation respectively.[1,2] The study BE1116/7D-202KO was designed to establish efficacy in a group of patients with congenital VKD factor deficiency, but recruited only two patients.

Pivotal Trials - Acquired VKD Factor Deficiency

Study BE1116-3001

This was a multi-centre, open-label, uncontrolled, prospective Phase III study evaluating the efficacy and tolerability of Beriplex in the reversal of oral anticoagulation (that is, acquired Vitamin K-dependent factor deficiency). From a planned sample size of 40 subjects, an enrolment of 44 patients was achieved, of whom 43 patients received the study treatment and were evaluable. These 43 patients formed the intention-to-treat efficacy population and the safety population. The study was conducted between October 2005 and November 2006, and was in accordance with GCP principles.

Male and female adults over the age of 18 who had an INR > 2 due to oral anticoagulation (coumarin or its derivatives) were recruited. To be included in the trial, these patients required either emergent surgical or urgent invasive diagnostic interventions, or had an acute haemorrhage where normalization of the INR was required. Patients were assigned in an unblinded fashion to one of three treatment groups, according to baseline INR. Patients with a baseline INR of 2 – 3.9 (hereafter "Group 1") received 25 IU/kg of the study drug, patients with a baseline INR of 4 – 6 (hereafter "Group 2") received 35 IU/kg, and patients with a baseline INR of greater than 6 (hereafter "Group 3") received 50 IU/kg. The maximum dose was 5,000 IU of study drug. In all cases, the calculated dose was to be rounded up to the nearest full vial (for example, a patient with an INR of 2 and weight of 65kg would receive 1,625 IU, rounded up to three 500 IU and one 250 IU vial or 1,750 IU). All infusions were to be given at a rate no greater than 210 IU/min. All patients also received vitamin K by slow IV injection according to local clinical practice guidelines.

Forty-four patients were enrolled at 15 centres in Europe and Israel, although one patient was discontinued without receiving any study drug and was excluded from the analysis. Patient demographics were as expected for a study of this design and, where given, were not significantly different between the three dosing groups. Three oral anticoagulants were in use by the patients in the trial, including acenocoumarol (40%), phenprocoumon (40%) and warfarin (20%). Two-thirds were receiving this for prophylaxis or treatment of thromboembolic events including atrial fibrillation (44%), deep vein thrombosis (12%) and pulmonary embolism (9%). Common concomitant medications included agents acting on the renin-angiotensin system (44%) and diuretics (37%). The most common indication for anticoagulation reversal was for emergent surgery (60%), where the most common procedure was incision and drainage and vascular surgery (5 patients each). Acute bleeding accounted for the remaining 40% of the reversal indications, and gastrointestinal bleeding was the most common cause here (8 patients).

Primary Efficacy Outcomes

The primary efficacy measure was a rapid decrease to INR≤ 1.3 within 30 minutes. This endpoint was chosen because it was appropriately "urgent", and corresponds with a level of reduced risk for surgical procedures. This was achieved in 40 of the 43 patients. For the three patients who did not achieve an INR of ≤ 1.3 at thirty minutes, the recorded INR was 1.4; depending on clinical context this could be considered adequate for the purposes of starting a surgical procedure. Two of these patients were from Group 1, and one was from Group 2. There were no significant differences in treatment success by dose group, sex, age or surgical indication.

Secondary Efficacy Outcomes

The secondary efficacy measures comprised *in vivo* recovery of the specific coagulation factors, and a physician's judgement of the adequacy of stopping ongoing bleeding or managing excessive bleeding during a surgical intervention.

An analysis of the outcomes of incremental *in vivo* recovery of individual factors was presented above, as these were also pharmacokinetic measures. Incremental *in vivo* recovery of each factor was generally adequate, and tended to decrease with increasing INR and therefore with increasing dose. The maximal median factor level after baseline exceeded 90% of normal in all groups for factors II and X and protein C. Despite small patient numbers in each group, the range of all values between 30 minutes and 48 hours was large, emphasizing the need for close monitoring of response over the 48 hours after treatment.

Clinical efficacy was judged by a physician to be "very good" (prompt cessation of bleeding, haemostasis during surgery near-normal), "good" (delayed cessation of bleeding up to 2 hours, mildly abnormal surgical haemostasis with slight oozing), "questionable" (cessation of bleeding after two hours, moderately abnormal surgical haemostasis with controllable bleeding), or "none" (total lack of effect on bleeding, severe surgical haemorrhage difficult to control).

Clinical efficacy was considered to be "very good" for 40 of the 43 patients. Two patients were assessed as "satisfactory"; both were from Group 3 (INR > 6) and had an INR of 1.0 at 30 minutes. These patients had rectal and retroperitoneal bleeding respectively. One patient from Group 1 was assessed as "questionable"; this patient had known bladder cancer and an INR of 1.4 at 30 minutes, 1.3 at 60 minutes and 1.4 at 180 minutes. Bleeding continued for two days after the infusion. The investigators considered this most likely from malignant epithelium, where bleeding would not be stopped only by normalizing the coagulation system with study drug. The evaluator feels this conclusion is reasonable.

Non-Pivotal Trials - Acquired VKD Factor Deficiency

Study BE1116/7D-201KO

This was a multi-centre, open-label, uncontrolled, prospective Phase II study evaluating the efficacy and tolerability of Beriplex in the treatment of acquired deficiency in factors II, VII, IX and X. From a planned sample size of 25 subjects, an enrolment of 30 patients was achieved, of whom 23 received a single dose and 7 received two doses of the study drug. These 30 patients formed the intention-to-treat efficacy population and the safety population. The study was conducted between 1995 and 1997, and was in accordance with GCP principles.

Male and female adults over the age of 18 were recruited. To be included in the trial, these patients required urgent surgical intervention during treatment with oral anticoagulants, treatment of acute haemorrhage due to overdose with oral anticoagulants, or severe liver disease with either acute haemorrhage, or before an invasive diagnostic or therapeutic intervention. In addition to the efficacy measures differing slightly from that of the pivotal study, the dosing schedule was also different, and different from that for which approval is sought. Hence, this study can be considered as "supporting" only, rather than pivotal. In severely ill patients with serious haemorrhage and before surgery with a high bleeding risk, a Quick's Value of 100% (corresponding to an INR of 1.0) was aimed for. Patients receiving oral anticoagulation received 1,000 IU before surgery, sometimes with an additional 500 IU dose, aiming for a Quick's Value of 40% - 50% (corresponding to an INR of approximately 1.6 – 1.9).

Thirty patients were enrolled at 3 centres in Europe, and all received their requisite study medication. The majority (70%) were male, and ages ranged from 29 to 88 years (median of 52 years). 8 patients receiving oral anticoagulation and 22 patients with severe liver disease were recruited. There were no significant differences between these two groups other than age – those with liver disease tended to be younger (range 29 to 65 years, median 45) than those receiving anticoagulation (range 61 to 88 years, median 77). The most frequent concomitant diseases were chronic liver disease with cirrhosis (16/30 patients, 53%), oesophageal varices and hypertension (9/30 patients, 30% respectively) and diabetes mellitus (6/30 patients, 20%).

Primary Efficacy Outcomes

The primary efficacy measures were largely pharmacodynamic. These included response (increase in individual factor activity per IU/kg body weight administered), *in vivo* recovery and increase in Quick's Value per IU/kg body weight (both defined above).

All factors demonstrated the expected rise in activity after infusion. Median response and IVR of factors II, VII and X were generally higher in patients receiving oral anticoagulation, whereas response and IVR of factor IX and protein C were higher in those with liver disease (Table 5).

Table 5 - Median response and IVR for each coagulation factor after first treatment (BE1116/7D-201KO)

Variable	Indication	Plasma activity (%) Baseline	C_{max}	Increase	Dose (IU/kg)	Response (Increase / dose/kg)	IVR (%)
F II	Liver disease	39.0	80.5	46.0	34.0	1.3	52.6
	Oral anticoag.	26.0	114.0	86.5	67.0	1.4	58.2
F VII	Liver disease	24.0	45.0	23.5	17.9	1.2	49.7
	Oral anticoag.	20.5	67.5	49.5	34.5	1.6	67.0
F IX	Liver disease	56.5	106.0	50.0	28.6	1.4	56.5
	Oral anticoag.	55.0	124.0	62.0	57.0	1.2	49.9
F X	Liver disease	48.0	110.0	60.5	43.7	1.4	56.9
	Oral anticoag.	11.5	121.5	111.0	84.7	1.7	69.3
Protein C	Liver disease	30.5	87.0	57.0	37.2	1.4	57.4
	Oral anticoag.	45.5	150.0	96.5	73.4	1.3	52.6

The Quick's Value rose as expected after infusion of the study drug. The median response to treatment was 1% increase per IU/kg body weight.

Seven patients required a second treatment with study drug in order to meet their required Quick's Value. One patient exhibited a decrease in the activity of all VKD factors, haematocrit and platelet count after the second dose. The investigators reported no clinical explanation for this finding and considered it a sampling error. Discarding this data, there were no significant differences in the efficacy measures between the first and subsequent treatment.

Secondary Efficacy Outcomes

The secondary efficacy outcomes were assessments of clinical efficacy. Judgements of clinical efficacy were given as "very good", "satisfactory", "questionable" or "none". These terms were not defined in the study report, but are presumed by the evaluator to be similar to the comparable secondary endpoint in Study BE1116-3001 (see above). Clinical efficacy was judged to be "very good" in 24/30 patients (80%) and "satisfactory" in 6/30 patients (20%). The clinical efficacy in those patients requiring a second treatment was rated as "very good" in 71% and "satisfactory" in 29%.

Study Preston et al., 2002[2]

This was a twin-centre, open-label, uncontrolled, prospective Phase II study evaluating the efficacy and safety of Beriplex in 42 patients receiving warfarin who were judged to require rapid reversal of their oral anticoagulation. The study was conducted between 1998 and 2001. Compliance with GCP principles was not stated.

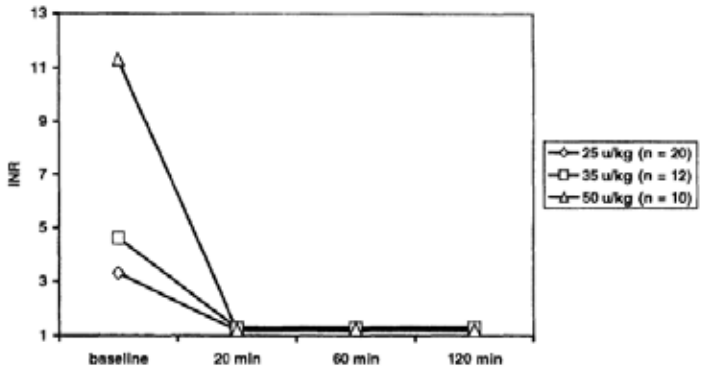
Male and female adults over the age of 18 were recruited. The only entry criteria for the trial were baseline treatment with warfarin, and a clinical judgement by the treating team that immediate reversal of oral anticoagulation was required. The dosing schedule was the same as in Study BE1116-3001 (and the schedule suggested for the proposed Product Information), namely a dose of 25, 35 or 50 IU/kg body weight, depending on the baseline INR (2.0 – 3.9, 4.0 – 6.0 and >6 respectively). All infusions were complete within ten minutes. One patient with an INR > 6 received only 35 IU/kg in light of concerns expressed by local cardiologists about the possibility of cardiac valve thrombosis. Although not explicitly stated, this appears to be the only significant deviation from protocol.

Baseline demographics were not presented in detail. The intention-to-treat population comprised 26 males and 16 females. Ages ranged from 26 to 83 years (median 70). The indications for reversal included gastrointestinal haemorrhage (17 patients), post head injury (5 patients), subdural haematoma (5 patients), miscellaneous spontaneous haemorrhage (5), emergent surgery (5 patients) and others.

Primary Efficacy Outcomes

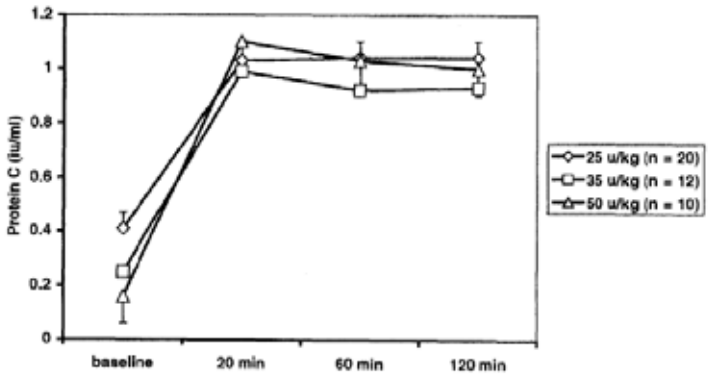
The primary outcome measures were entirely laboratory-based. In particular the INR, which was markedly elevated at baseline (median 3.98, range 2.0 – 27.6), was completely corrected (INR < 1.3) in 33/42 patients (79%) within 20 minutes. The remaining 9 patients all had INRs in the range of 1.3 to 1.9. (Figure 1)

Figure 1 - Change in INR over time by dose (Preston et al.)



The anticipated increase in median levels of the measured coagulation factors was seen in all cases; the protein C response (Figure 2) was typical of the sort of increase seen across all the measured VKD factors.

Figure 2 - Change in Protein C over time by dose (Preston et al.)



Secondary Efficacy Outcomes

Clinical measures of efficacy were not formally recorded, but the absence of haemorrhagic complications and the normalization of laboratory markers of coagulopathy strongly suggest cessation of bleeding.

Study Evans et al., 2001[1]

This was a small single-centre, open-label, uncontrolled, prospective Phase II study of the efficacy and safety of Beriplex in the treatment of major bleeding in 10 patients with a grossly elevated INR (of any cause). Inclusion criteria included an INR greater than 8.0, the need for urgent reversal of over-anticoagulation, and over the age of 18 years.

All patients received 5mg of vitamin K intravenously, and 30 IU/kg of Beriplex, regardless of initial INR. Blood tests (INR, factor levels and endogenous thrombin potential, alanine transaminase) and clinical examination were performed before treatment, and at 30 minutes, 6 to 8 hours, 24 hours and 48 hours after infusion. Patients were also examined specifically for clinical signs of deep vein thrombosis or pulmonary embolism until discharge from hospital.

The demographics of the population are not presented in detail. Eight of the ten patients were female, and the median age was 73 years (range 39 to 88). Six of the ten patients had an initial INR greater than 20; the remaining four were 8.9, 14.4, 15.8 and 18.0.

Primary Efficacy Outcomes

The primary outcome measures were clinical response, INR and specific factor levels at each time-point. All patients evidently had a satisfactory response to the study drug with cessation of bleeding in every patient by the six-to-eight-hour assessment. The median INR was 1.1 at 30 minutes and remained so until the 24 hour assessment. The upper range of INR at 48 hours was 1.7. Rapid and durable rises (at least for 24 hours) were seen for all the measured factors.

Secondary Efficacy Outcomes

The endogenous thrombin potential (ETP) was included as a surrogate marker for hypercoagulability. This measure has been used to assess hypercoagulability in patients with heritable thrombophilias and in those receiving oral anticoagulant therapy. The literature describes an increase in ETP to greater than 110% of normal as indicative of thrombotic tendency, and of 20% to 40% as indicative of effective anticoagulation. The threshold of greater than 110% of normal was crossed by one patient at the 30 minute timepoint.

Non-Pivotal Trials - Congenital VKD Factor Deficiency

Study BE1116/7D-202KO

This study was a multi-centre, open-label, uncontrolled, prospective Phase II study of the efficacy and safety of Beriplex in the treatment of acute bleeding or prophylaxis before surgical or dental procedures in patients with congenital isolated or combined deficiency in the VKD clotting factors. Unfortunately its sample size of two patients highlights the difficulties of studying therapies in this population, and prevents any conclusions regarding efficacy and safety. An enrolment of 5 to 10 patients had been planned. The trial was intended to be conducted over a number of German sites in 1995 and was in accordance with GCP principles.

Inclusion criteria, other than a congenital deficiency of one or more of the components of the prothrombin complex, were age greater than 18 years and one of ongoing acute bleeding, the need for surgical or dental intervention, or another indication for prophylactic substitution of one or more factors of the prothrombin complex. The dosage used was different from that proposed in the Product Information, and was given by the formula of body weight (in kg) multiplied by the target increase of factor IX (in percent) multiplied by 1.2. There was no co-administration of vitamin K in this trial.

Both patients enrolled in the trial were males suffering from severe haemophilia B (factor IX deficiency).

Primary Efficacy Outcomes

The primary endpoints were as for Study BE1116/7D-201KO, namely specific factor levels, response (increase per dose/kg) and *in vivo* recovery (previously defined). Both patients displayed the expected increases in all factors. The Quick's Value for both patients increased to 100% at the 10-minute time-point and remained greater than 80% until the last measurement (at four hours). The aPTT decreased immediately after infusion from greater than 60 seconds to 40 seconds and remained at this level throughout the observation period.

Secondary Efficacy Outcomes

Clinical efficacy was judged to be very good by the treating physician at the end of the study. For one patient in whom the study drug was given as bleeding prophylaxis, no bleeding was reported during the trial.

Safety

Pivotal Studies - Acquired VKD Factor Deficiency

Study BE1116-3001

Drug Exposure and Overview of Adverse Events

Of the 44 patients enrolled in the study, 43 received at least a portion of the intended dose of study drug, and formed the safety population. The median duration of the infusion was 12 minutes. The median dose was 2,600 IU.

Overall, 25/43 patients (58%) in the safety population experienced at least one adverse event, but only two patients experienced an adverse event that was rated as possibly related to the study drug. The most common adverse events (Table 6) were wound complications (7/43 patients, 16%), pyrexia (5/43 patients, 12%) and nausea (4/43 patients, 9%).

Table 6 - Most frequent adverse events (BE1116-3001)

Adverse event	Number of subjects (%)
Wound complication	7 (16)
Pyrexia	5 (12)
Nausea	4 (9)
Hypertension	2 (5)
Insomnia	2 (5)
Vomiting	2 (5)
Thromboembolic events*	2 (5)

In total, 9/43 patients (21%) experienced a severe adverse event (CTC grade 3 or 4), of which only one – pulmonary embolism – was considered possibly related to treatment. No severe adverse event was seen with an incidence of more than one occurrence.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

There were three deaths recorded as treatment-emergent adverse events, or occurring between the giving of informed consent and the first virus safety follow-up visit at day 7-10. One of these deaths was considered possibly related to treatment. This patient was a 70 year old male with a perforated gastric ulcer in the context of metastatic gastric cancer, who received 3,640 IU of study drug. During his course of treatment he required a second infusion of study drug; two hours thereafter he developed shortness of breath which was rapidly fatal. Pulmonary embolism was the clinical diagnosis (no autopsy was performed). The investigators considered this possibly related to treatment with the study drug (especially because of the close temporal relationship between dose and death), although it must be acknowledged that other contributing factors may have been involved. Two patients died during the follow-up period (of respiratory failure and encephalopathy respectively); both were considered unrelated to treatment.

Six patients (14%) experienced a serious adverse event, of which only one (the pulmonary embolus discussed above) was considered possibly related to treatment.

No patient was discontinued from the study due to an adverse event.

Adverse Events of Special Interest

Two adverse events were of particular interest, given the existing experience with PCCs. Thromboembolism is a known complication of PCC treatment, although it is often difficult to differentiate between a complication of the study drug and a complication of the underlying thrombosis risk that is usually the indication for oral anticoagulation. Two patients experienced three instances of thromboembolism: in addition to the already-mentioned patient with pulmonary embolism, a 74-year-old female patient with atrial fibrillation and a past history of arterial embolism developed a further femoral arterial thrombosis and right middle cerebral artery embolism two days after treatment. She required reversal of her anticoagulation for haemorrhage, and the adverse event was considered unrelated to treatment with the study drug.

Although the manufacturing process for the study drug was designed to minimize the chance of viral transmission, it remains another risk of PCC treatment. Aside from one possible seroconversion for anti-hepatitis A IgG, there were no seroconversions for any of the viruses tested during follow-up. This patient tested negative for anti-hepatitis A IgG at baseline but became positive at day 29-32 and remained so at day 78-92. There was no viraemia at any stage, nor were there clinical symptoms or a history of vaccination during the study period. The pools of plasma used for manufacturing all batches of the study drug were tested

negative for hepatitis A RNA, and the particular batch of study drug involved in this case of seroconversion was also used to treat seven other patients who were IgG negative, and remained so. The absence of viraemia or IgM antibodies makes transmission of hepatitis A very unlikely but the possibility cannot be excluded.

Laboratory Abnormalities, Vital Signs and Physical Examination

Median values for haemoglobin and haematocrit were below or at the lower limit of normal even at baseline, as would be expected for a population which includes those with acute haemorrhage. Median values for platelets remained normal until 24 hours after treatment.

Thrombogenicity was assessed be measuring concentrations of prothrombin fragments 1 and 2, thrombin-antithrombin complexes, and d-dimer.

Non-Pivotal Studies - Acquired VKD Factor Deficiency

Study BE1116/7D-201KO

Drug Exposure and Overview of Adverse Events

The safety population comprised all 30 patients who had received their scheduled dose of study drug. The actual dose of study drug administered depended on the clinical scenario and Quick's Value, as described above. Doses ranged from 1000 to 4000 IU for the first treatment (mean ± SD of 1940 IU ± 740 IU) without significant differences between those with liver disease and those receiving oral anticoagulation. Patients received a median of 236 IU/min of study drug, and patients receiving oral anticoagulation on average received their drug more than twice as fast as those with liver disease (medians 375 IU/min versus 150 IU/min respectively).

Overall, 7/30 patients (23%) in the safety population experienced one adverse event each, but only one was thought to be possibly related to the study drug. The most common adverse events were suspected hepatitis A infection (3/30 patients, 10%), abnormal laboratory tests, liver failure, vomiting and shock (one patient each, 3%).

Two adverse events were rated as severe (CTC grade 3 or 4), neither of which was considered treatment-related.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

Two deaths were reported within seven days of receiving the study drug, these also being the two adverse events rated as "severe" and the only serious adverse events. Neither was considered related to the study drug but rather to underlying disease. Narratives of these events could not be located by the evaluator in the submitted data. One appears to involve a 32-year-old male patient who died of hepatic encephalopathy, and another was a 60-year-old male who developed septic shock and multi-organ system failure. There were no discontinuations due to adverse events.

Adverse Events of Special Interest

No adverse events were described *a priori* as being of special interest, other than viral safety. In this case, assessments of the relevant sera for hepatitis A, B and C, and the human immunodeficiency virus were performed at baseline and at six months. The analysis is incomplete, in that for almost half the patients (14/30) no second serological assessment was made. In 8 cases this was due to death during the six months between assessment and serology, and 6 patients were lost to follow-up.

Six patients exhibited a change in their serological status to one or more viruses, all of whom had underlying liver disease. Changes from positive at baseline to negative at 6 months are

not clinically relevant. One change in hepatitis B surface antibody is almost certainly explained by chronic hepatitis B at baseline. Three patients were negative for hepatitis A antibodies at baseline but became positive at 6 months; none of the three were accompanied by clinical symptoms, and two subsequently became negative again, suggesting passive immunization with immunoglobulin rather than viral transmission, although this cannot be proven. All three received study drug from the same batch number, but this batch did not show a positive PCR signal for hepatitis A virus. Viral transmission therefore seems unlikely.

Laboratory Abnormalities, Vital Signs and Physical Examination

Laboratory measures included haematology, and a number of coagulation markers including thrombin-antithrombin complexes, prothrombin fragments 1 and 2, d-dimers, factors I, V, VIIa, VIII, antithrombin III and aPTT.

Study Preston et al., 2002[2]

Drug Exposure and Overview of Adverse Events

All 42 patients receiving any dose of the study drug were included in the safety analysis. Detailed patient listings were not presented, nor did the submission contain elsewhere the data necessary to reconstruct exposure to the study drug. It is declared, however, that 20 patients received 25 IU/kg, 12 patients received 35 IU/kg and 10 patients received 50 IU/kg.

Haematology and thrombogenicity were the only safety parameters presented in the report; adverse events were not tabulated. There was no clinical evidence of disseminated intravascular coagulation (DIC) in any of the patients treated with the study drug.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

Eight patients died within seven days of treatment. The causes of death were heterogeneous, including non-operative subdural haematoma, thrombotic stroke, cardiac failure, staphylococcal septicaemia, acute pancreatitis, acute renal failure, asystolic cardiac arrest, and intracranial haemorrhage. Where performed, there was no post-mortem indication of arterial or venous thromboembolism in any case. In the case of death from thrombotic stroke, the indication for Beriplex treatment was for emergent leg amputation for severe atherosclerotic vascular disease – the likelihood of significant concurrent cerebrovascular atherosclerosis is a confounder. In the other deaths it appears that underlying pathology, and not study drug treatment, was responsible for the patients' demise.

Adverse Events of Special Interest

Coagulation activation, DIC, and thrombovascular events were considered of special interest. Platelet counts, d-dimer, fibrinogen and antithrombin assays were surrogate markers. Antithrombin levels were reduced at baseline in many patients for reasons that were unclear, but this did not seem to be associated with clinical features or other markers of DIC, such as elevations in d-dimer.

In one patient, antithrombin fell from 0.77 IU/mL to 0.45 IU/mL at twenty minutes and was accompanied by a reduction in fibrinogen but no increased in d-dimer. This may have represented coagulation activation, but the investigators offer haemodilution as another possible explanation.

Laboratory Abnormalities, Vital Signs and Physical Examination

Median platelet values fell after treatment in the 35 IU/kg group, although this appeared not to be clinically significant and post-treatment counts remained within the normal range.

Platelet counts remained normal for patients treated with the higher or lower dose of study drug.

Study Evans et al., 2001[1]

Drug Exposure and Overview of Adverse Events

This report did not present a detailed analysis, but made a few brief comments. All ten patients were exposed to the study drug at a dose of 30 IU/kg. The range of actual doses given is not presented. Haematology and thrombogenicity (as expressed by the endogenous thrombin potential or ETP) were the only safety variables recorded.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

There were no deaths, serious adverse events or discontinuations recorded.

Adverse Events of Special Interest

One patient had an increase of ETP beyond 110% of normal, a threshold proposed in the literature as representing thrombotic tendency. This did not correspond to any clinical suspicion of either deep venous thrombosis or pulmonary embolism.

Laboratory Abnormalities, Vital Signs and Physical Examination

Two patients developed thrombocytopenia without clinical evidence of disseminated intravascular coagulation. Two patients had abnormal levels of alanine transaminase on admission, of whom one was subsequently found to have a rectal cancer with hepatic metastases.

Non-Pivotal Studies - Congenital VKD Factor Deficiency

Study BE1116/7D-202KO

Drug Exposure and Overview of Adverse Events

This trial exposed two patients to the study drug, both of whom received 2,000IU. The design of this trial did include a formal mechanism for auditing adverse events; none were reported.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

No deaths, serious adverse events or discontinuations occurred in this trial.

Adverse Events of Special Interest

Viral safety was the only adverse event defined *a priori* as being of special interest. Both patients were positive for antibodies to hepatitis B core antigen and hepatitis C virus at baseline, and one also for the human immunodeficiency virus. The investigator abstained from repeating viral serology at six months, given that no meaningful conclusions would be able to be drawn from their results.

Laboratory Abnormalities, Vital Signs and Physical Examination

Moderate increases above baseline were seen at the 10 minute time-point, in prothrombin fragments 1 and 2 and thrombin-antithrombin complexes. Both had returned to baseline at four hours, without clinically meaningful sequelae.

Healthy Subjects, from Pharmacokinetic Studies

Study BE1116-1001

Drug Exposure and Overview of Adverse Events

All of the 15 patients enrolled in the study received at least a portion of the intended dose of study drug and comprised the safety population. The median duration of the infusion was 19 minutes (range 17 – 23 minutes). The exact dose ranged from 1758 – 2830IU, corresponding to a dose of 30IU/kg as the protocol required.

Only one of the 15 subjects experienced an adverse event, this being an episode of nasopharyngitis which was mild, self-limiting and resolved without sequelae; it was considered unrelated to the study drug. There were no severe adverse events.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

The study reported no deaths, serious adverse events, or discontinuations due to adverse events.

Adverse Events of Special Interest

Thrombogenicity and viral safety were considered of special interest.

Thrombogenicity was assessed by assays of prothrombin fragments 1 and 2, thrombin-antithrombin complexes and d-dimers. Concentrations of the prothrombin fragments and thrombin-antithrombin complexes were markedly elevated immediately following infusion, while d-dimers remained constant at each time-point. Interestingly, the concentration of thrombin-antithrombin complexes in this population of healthy subjects was significantly higher than the quoted normal range at baseline – the reason for this is not clear. The investigators point out that the study drug contains both the prothrombin fragments and thrombin-antithrombin complexes, and the half-lives of both these markers fits well with the decay in both levels seen at 3 and 24 hours. It is acknowledged that in three cases these results could be interpreted as an activation of coagulation, although this was not noted clinically.

Viral safety was investigated by baseline and repeat testing of antibodies to HIV, hepatitis A, hepatitis B, hepatitis C and parvovirus B19. There were no seroconversions from negative pre-infusion to positive post-infusion for any of the antibodies assayed.

Laboratory Abnormalities, Vital Signs and Physical Examination

There were no significant changes in haematology or biochemistry, nor were there any clinically significant changes to physical examination or vital signs over time.

Clinical Summary and Conclusions

Pharmacokinetics

The pharmacokinetics of Beriplex was examined in 15 healthy volunteers given a single dose of 50 IU/kg of the study drug. Data from Study BE1116-1001 indicate that a sufficient increase of relevant plasma factor levels can be expected in subjects after a single infusion of 50 IU/kg Beriplex. The relatively short half-life of factor VII (median 5.0 hours, range 2.1 – 9.2 hours) suggests that repeated infusions may be needed to maintain sufficient activity of this factor, for example in the perioperative context. Data from Study BE1116-3001 suggest that there is a sufficient increase of relevant plasma factor levels when dosed according to the proposed schedule, although it was noted that factor VII achieved only 55% and 69% recovery in the 50 IU/kg (INR >6) and 35 IU/kg (INR 4-6) groups, respectively. Significant variability of pharmacokinetic parameters was noted between subjects, suggesting a need to monitor response (in terms of global tests of the prothrombin complex such as the INR) during treatment.

Pharmacodynamics

The clinical portion of the submitted dossier includes no studies of pharmacodynamics. The INR and Quick's Value are acceptable surrogate pharmacodynamic measures of the effects of acquired VKD factor deficiency (such as oral anticoagulation therapy or liver disease) on normal human coagulation. The INR and Quick's Value are also acceptable surrogate measures of the effects of VKD factor replacement on human coagulation. Clinical pharmacodynamic studies of patients with congenital deficiencies of VKD clotting factors are significantly challenged by the rarity of the condition; however, experience with other PCCs suggests that specific recombinant factor replacement is probably superior.

Efficacy

Taken together, the clinical studies submitted in the application provide acceptable evidence for the efficacy of Beriplex in the rapid treatment of acquired VKD factor deficiency. The studies reporting plasma levels of component factors and *in vivo* recovery demonstrated that a single infusion of Beriplex rapidly increased plasma levels of its components to normal or near-normal levels, although this effect was less reliable beyond 24 hours. Where clinical judgement of adequacy was used as an endpoint (BE1116-3001 and BE1116/7D-201KO), Beriplex was considered effective in 42 out of 43 and 30 out of 30 patients respectively. The pivotal study BE1116-3001 provides evidence of the rapid reversal of oral anticoagulation using the dosing schedule proposed for Beriplex, as evidenced by the normalization of INR (≤ 1.3) within 30 minutes in 40 out of 43 patients treated. Efficacy was also demonstrated by study BE1116/7D-201KO in a further 30 patients with acquired deficiency of the VKD coagulation factors, including 22 patients with severe liver disease, although this study did not use the dosing schedule proposed for Beriplex. The published, peer-reviewed and manufacturer-sponsored studies by Preston et al. (2002) and Evans et al. (2001) provided supporting evidence of efficacy in 52 patients requiring urgent reversal of oral anticoagulation.[1,2] The study BE1116/7D-202KO did not recruit sufficient numbers of patients with congenital VKD factor deficiency to allow conclusions of efficacy to be drawn.

Safety

The safety of Beriplex was established in four clinical trials formally reporting adverse events (BE1116-3001, BE1116-1001, BE1116/7D-201KO and BE-202KO, a population of 90 patients) and supported by two published manufacturer-sponsored studies (a further 52 patients). The number of patients experiencing one or more adverse event is consistent with the comorbidities of the population being studied; only 3 patients experienced an adverse event possibly related to the study drug. The numbers of serious adverse events and deaths (15) were not unexpected in a population with moderate background risk (for example, liver disease, need for anticoagulation) and often life-threatening intercurrent illness (for example, haemorrhage). Two serious adverse events (pulmonary embolism, thrombotic stroke) were possible related to Beriplex but in both cases there were significant confounders – the study drug could be considered as one of several factors contributing risk. Although some markers of thrombogenicity were transiently elevated, this was not clearly associated with clinical thromboembolism. Of the two instances of thromboembolism (the two serious adverse events just listed) both were in high-risk patients with many contributing risk factors. The only instances of seroconversion to any of the viruses studied was to hepatitis A, and in several cases this was transient, suggesting passive immunisation rather than transmission; none of the batches tested was positive for any of the viruses studied

Conclusion

The submission includes clinical data that favour the registration of Beriplex for the urgent treatment and prophylaxis of bleedings in acquired VKD factor deficiency, whether it be from oral anticoagulation or severe liver disease. Beriplex may offer clinical advantages over other PCCs marketed in Australia, in particular over Prothrombinex-VF which contains only minimal amounts of factor VII. The leading current local guidelines specifically recommend the co-administration of FFP with Prothrombinex-VF, for this very reason. Treatment with Beriplex may obviate the need for FFP, with its limitations in availability, compatibility, relatively slow time-to-effect and safety. As such, Beriplex appears to be a drug with established efficacy and real clinical utility. Furthermore, the drug has a favourable safety profile. Although thrombogenicity remains a risk (both of the drug treatment and of the

underlying condition being treated), this risk appears small and should be weighed against the benefit of therapy by the treating clinician.

The proposed dosing schedule in this population is applicable to contemporary Australian clinical conditions and is supported by the pivotal study.

Supporting the registration of Beriplex for the treatment and prophylaxis of bleedings in congenital VKD factor deficiency is more problematic. The challenges of studying treatments in such rare diseases are acknowledged. There is sufficient pharmacokinetic evidence tendered in this submission to suggest that Beriplex ought to be effective in this population, but this has not been demonstrated satisfactorily in factor IX deficiency, or at all in factor II, VII or X deficiency. Moreover, there exist significant theoretical misgivings about such an approach since Beriplex would likely produce a surplus of factors not deficient before treatment, and this may be associated with increased thrombotic risk.

On balance, the evaluator recommends approval to register Beriplex for the treatment and prophylaxis of bleedings in the acquired deficiency of the prothrombin complex coagulation factors. The evaluator cannot support its approval for use in congenital VKD factor deficiency because its efficacy and safety in this group – although likely – has not been satisfactorily proven.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The application was reviewed by the Pharmaceutical Subcommittee (PSC) on 21 September 2009. The PSC endorsed the evaluator's questions which have now been resolved. The product was adequately characterised and process validation including viral and prion clearance were satisfactory. Shelf-life is 3 years. The plasma source complies with the Ph.Eur. monograph and the plasma master file was acceptable to TGA. There were no objections to approval on biopharmaceutical or quality grounds.

Two labelling exemptions were granted. As with other biological products, initial batch monitoring by TGA is recommended until the consistency of the product is demonstrated.

Nonclinical

Nonclinical data were limited due to the product being human-derived. Thrombogenicity was observed in rats and rabbits at 5- and 2-fold the maximum recommended human dose based on factor IX activity. Immune reactions were seen in rabbits. There were no nonclinical objections to approval.

Clinical

Pharmacokinetics

Trial BE1116-1001 assessed the pharmacokinetics of Beriplex P/N in 15 healthy subjects after a single IV dose of 50 IU/kg. Table 7 lists results for half-life and incremental recovery of the coagulation factors. Factor VII half-life was short.

Table 7: Beriplex P/N Pharmacokinetic Parameters in Healthy Subjects - Median (Range)

	Half-Life h	**Recovery %/IU/kg**
Factor II	60 (25-135)	2.1 (1.8-2.5)
Factor VII	4(2-9)	2.4 (1.7-3.3)
Factor IX	17 (10-127)	1.6 (1.1-2.6)
Factor X	31 (17-44)	2.1 (1.6-3.2)
Protein C	47 (9-122)	2.8 (2.2-3.3)
Protein S	49 (33-83)	not done

Trial BE1116-3001 (the pivotal efficacy trial) assessed the pharmacokinetics of Beriplex P/N in 43 subjects with acquired deficiency of vitamin K dependent coagulation factors as a result of anti-coagulation. Subjects received a single IV dose based on their INR. The median maximal level exceeded 90% of normal for factors II and X and protein C. There was considerable variability (Table 8). Recovery decreased with increasing INR and Beriplex P/N dose.

Table 8: Beriplex P/N Pharmacokinetic Parameters in Subjects with Acquired Deficiency of Coagulation Factors - Median (Range)

	Dose *IU/kg*	**Baseline** *% normal*	**Maximal** *% normal*	**Recovery** *%/IU/kg*
Factor II	25	26 (14-60)	90 (46-147)	2.0 (1.3-3.1)
	35	12 (4-13)	100 (30-145)	1.9 (1.4-2.8)
	50	4 (4-24)	108 (32-155)	1.5 (1.0-2.3)
	all			1.9 (1.0-3.1)
Factor VII	25	23 (10-73)	83 (18-146)	1.7 (0.9-2.7)
	35	16 (4-46)	69 (8-114)	1.7 (1.1-2.5)
	50	4 (4-26)	56 (4-100)	1.1 (0.5-2.1)
	all			1.7 (0.5-2.7)
Factor IX	25	43 (26-113)	104 (24-183)	1.3 (0.9-3.4)
	35	23 (12-40)	78 (25-160)	1.1 (0.9-1.9)
	50	15 (10-24)	88 (36-143)	1.0 (0.7-1.7)
	all			1.3 (0.7-3.4)
Factor X	25	13 (4-50)	94 (33-190)	1.9 (1.5-2.9)
	35	4 (4-9)	117 (32-185)	1.6 (1.5-3.0)
	50	4 (4-24)	142 (40-223)	1.6 (1.1-2.6)
	all			1.8)1.1-3.0)
Protein C	25	43 (27-100)	110 (54-180)	2.2 (1.6-3.1)
	35	37 (14-62)	133 (40-171)	1.9 (1.7-2.8)
	50	25 (9-54)	132 (41-202)	1.8 (1.3-2.4)
	all			2.1 (1.3-3.1)
Protein S	25	37 (22-73)	78 (36-108)	2.8 (1.5-4.5)
	35	17 (8-38)	60 (15-101)	1.9 (1.0-2.5)
	50	22 (16-28)	95 (27-133)	2.0 (1.0-2.5)
	all			2.3 (1.0-4.5)

Trial BE1116/7D-202KD assessed the pharmacokinetics of Beriplex P/N in 2 subjects with acquired factor IX deficiency. The subjects were males aged 25 and 27 years. Subjects received a prophylactic IV dose according to the formula: Dose = Body Weight (kg) x Target

Increase in Factor IX x 1.2. As in acquired deficiency, there was considerable variability in pharmacokinetic parameters (Table 9).

Table 9: Beriplex P/N in Subjects with Congenital Deficiency of Factor Ix – *in vitro* recovery %/IU/kg

	Baseline *% normal*		**Maximal** *% normal*		**Recovery** *%/IU/kg*	
	Subj 1	**Subj 2**	**Subj 1**	**Subj 2**	**Subj 1**	**Subj 2**
Factor II	86	148	124	185	2.0	2.6
Factor VII	96	113	104	164	1.8	8.7
Factor IX	3	30	2	53	1.3	3.3
Factor X	105	176	162	243	1.7	2.7
Protein C	76	134	90	151	1.8	2.6

Efficacy

The pivotal efficacy trial (BE1116-3001) of Beriplex P/N was uncontrolled. Subjects required urgent reversal of acquired deficiency of vitamin K dependent coagulation factors. Sixty percent of subjects were undergoing surgery and 40% had acute bleeding. Subjects received vitamin K injection in addition to Beriplex P/N. The primary efficacy measure, decrease in INR to ≤ 1.3 within 30 minutes, was achieved by 40 subjects (93%) (Table 10). Three subjects (7%) did not achieve the efficacy measure but were close with INR of 1.4. Efficacy was rated "very good" by the physician in 40 subjects (93%). In two subjects who received 50 IU/kg efficacy was satisfactory. One had rectal and the other retroperitoneal bleeding. Efficacy in one subject who received 25 IU/kg was questionable. This subject had bladder cancer and bleeding continued for 2 days, most likely from malignant epithelium.

Table 10. Beriplex P/N Efficacy in Subjects with Acquired Deficiency of Coagulation Factors

Dose *IU/kg*	**No. Subjects**	**% with INR Response[1]**	**% with "Very Good" Rating[2]**
25	26	92	96
35	7	85	100
50	10	100	80
Overall	43	93	93

[1] Decrease in INR to ≤ 1.3 within 30 minutes. [2] Prompt cessation of bleeding or near-normal haemostasis during surgery (as rated by physician).

There were three supportive trials. The Preston trial (n=42) used the same dose schedule in a similar population requiring urgent reversal of anticoagulant. All subjects also received intravenous vitamin K. The target INR of < 1.3 was achieved in 33 patients (79%) within 20 minutes of Beriplex P/N. The other patients achieved INRs of 1.3-1.9. Clinical efficacy was not assessed. Trial BE1116/7D-201KO (n=30) used a Beriplex P/N dose of 1,000 IU with another 500 IU if necessary in an acquired deficiency population of 22 subjects with severe liver disease and 8 subjects on anticoagulants. Efficacy was assessed by the physician as very good in 80% and satisfactory in the remainder. After a second dose (n=7), efficacy was very good in 71% and satisfactory in 29%. The Evans trial in 10 subjects requiring urgent reversal of anticoagulation used a Beriplex P/N dose of 30 IU/ kg with 5 mg IV vitamin K. Cessation of bleeding occurred within 8 h of treatment in all subjects.

Trial BE1116/7D-202 KO assessed Beriplex P/N in two subjects with severe haemophilia B (congenital factor IX deficiency). The dose calculation is given under *Pharmacokinetics* above. Both subjects achieved a Quick's Value of 100% (equivalent to INR of 1.0) within 10 minutes of Beriplex P/N and it remained above 80% for at least 4 h. Efficacy was assessed as very good by the physician in both subjects.

Safety

There were safety data from 142 subjects receiving Beriplex P/N in six trials. Most subjects (n=135) received a single dose only. In the pivotal trial, two subjects (5%) had adverse events possibly related to Beriplex P/N – one a fatal pulmonary embolism and the other increased prothrombin fragments 1 and 2 (F_{1+2}) indicating high risk of thrombosis. In trial BE1116/7D-201KO, one subject (3%) had an adverse event possibly related to Beriplex P/N – vomiting. There were minimal safety data from the other trials, two being published reports. In one of the published reports (Preston), one subject (2%) had a fatal thrombotic stroke possibly related to Beriplex P/N.

Possibly related post-marketing events were portal vein thrombosis with fatal outcome, acute myocardial infarction, disseminated intravascular coagulation, anaphylactic reaction and allergic reaction.

The evaluator supported registration for acquired deficiency but not congenital deficiency.

Risk-Benefit Analysis

In subjects with congenital and acquired deficiency of vitamin K dependent coagulation factors, there was considerable variability in the pharmacokinetic parameters of the factors in an infusion of Beriplex P/N. Factor VII half-life was short indicating that repeated infusions of Beriplex P/N may be required in patients with factor VII deficiency. However, the need for repeated infusions must be balanced against the increased risk of thrombosis due to accumulation of factors with longer half-lives.

Efficacy in acquired deficiency was adequately demonstrated in the pivotal efficacy trial (BE1116-3001) and three supportive trials. The recommended dose of Beriplex P/N is 25-50 IU/kg based on INR. This was the dose in the pivotal trial. In two of the supportive trials, lower doses of Beriplex P/N appeared to be as effective as 25-50 IU/kg. Due to variable pharmacokinetics, the dose of Beriplex P/N should be individualised and response closely monitored.

In congenital deficiency, there were only two subjects, both with factor IX deficiency. Efficacy was rated very good in both. Despite the good results, the trial was insufficient to assess the efficacy of Beriplex P/N in congenital vitamin K dependent coagulation factor deficiencies. The dosage recommendations in the product information are based on recovery data from patients with acquired deficiencies (trial BE1116-3001) and may not necessarily apply for patients with congenital deficiency. In their response to the clinical evaluation, the sponsor acknowledged the insufficient evidence in congenital deficiency and withdrew this indication from their application.

Beriplex P/N was generally well tolerated. The major risk is thromboembolism. There were two reports of thrombosis (both fatal) in the clinical trials and three (one fatal, others with outcome unknown) in post-market spontaneous reports with a possible relationship to Beriplex P/N. The risk of thrombosis is likely to increase with increasing dose. There was insufficient data to assess this. The precautionary statements in the proposed product information are adequate. There were no data in children.

The Delegate recommended registration of Beriplex P/N (human prothrombin complex) powder for injection vials, containing 250 and 500 IU of factor IX, subject to finalisation of product information, for the indication:

Treatment and perioperative prophylaxis of bleedings 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

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the delegate's proposal.

In making the recommendation, the ADEC was satisfied that efficacy in treating acquired deficiency of the prothrombin complex coagulation factors was adequately demonstrated in the pivotal efficacy trial (BE1116-3001) and three supportive trials. The Committee noted that Beriplex is generally well tolerated. The major risk is thromboembolism, which is likely to increase with increasing dose, however the Committee noted that this is not unexpected and the precautionary statements in the product information are adequate.

Recommendation

Based on review of quality, safety and efficacy data, TGA approved the registration of Beriplex P/N powder for injection vial containing human prothrombin complex 250 IU and 500 IU indicated for:

> *Treatment and perioperative prophylaxis of bleedings 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.*

Attachment 1. Product Information

Product Information

Beriplex™ P/N

Australia

NAME OF THE MEDICINE

Human prothrombin complex, powder for injection.

DESCRIPTION

Beriplex P/N is presented as a powder, containing human prothrombin complex, in packs of 250 IU and 500 IU factor IX, for reconstitution with a vial of diluent. The product contains the following IU of the human coagulation factors tabled below:

Name of the ingredients	Content after reconstitution (IU/mL)	Beriplex P/N 250 content per vial (IU)	Beriplex P/N 500 content per vial (IU)
Active Ingredients			
Human coagulation factor II	20 – 48	200 – 480	400 – 960
Human coagulation factor VII	10 – 25	100 – 250	200 – 500
Human coagulation factor IX	20 – 31	200 – 310	400 – 620
Human coagulation factor X	22 – 60	220 – 600	440 – 1200
Other active ingredients			
Protein C	15 – 45	150 – 450	300 – 900
Protein S	12 – 38	120 – 380	240 – 760

The total protein content is 6 – 14 mg/mL of reconstituted solution.

The specific activity of factor IX is 2.5 IU per mg total protein.

The activities of all coagulation factors as well as Protein C and S (antigen) have been tested according to the current valid international WHO-Standards.

The list of excipients in Beriplex P/N powder includes: Heparin, Human albumin, Human antithrombin III, Sodium chloride, Sodium citrate and HCl or NaOH (in small amounts for pH adjustment).

The vial of diluent contains Water for Injections.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors II, VII, IX and X in combination. [ATC code: B02B D01]

The coagulation factors II, VII, IX and X, which are synthesised in the liver with the help of vitamin K, are commonly called the prothrombin complex. In addition to the coagulation factors Beriplex P/N contains the vitamin K dependent coagulation inhibitors Protein C and Protein S.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue thromboplastin factor-factor VIIa complex 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 further ingredients, the coagulation inhibitors Protein C and Protein S, are also synthesised in the liver. The biological activity of Protein C is enforced by the cofactor Protein S.

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

Acquired deficiency of the vitamin K dependent coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitamin K dependent coagulation factors and a clinically 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.

Pharmacokinetic properties
Plasma half-life is indicated as follows (data derived from a clinical study including 15 healthy volunteers administered a single intravenous dose of 50 IU/kg Beriplex P/N; median age 44, range 18-62):

	Half-life, hours Median (range)	***In Vivo* Recovery, % Median (range)**
Factor II	60 (25-135)	2.11 (1.75-2.54)
Factor VII	4 (2-9)	2.43 (1.67-3.27)
Factor IX	17 (10-127)*	1.57 (1.11-2.59)
Factor X	31 (17-44)	2.08 (1.64-3.19)
Protein C	47 (9-122)*	2.76 (2.16-3.31)
Protein S	49 (33-83)*	2.02 (1.46 – 2.70)

**terminal half-life; two-compartment-model*

Recoveries were up to 50% lower in a study in patients with acquired vitamin K dependent factor deficiency from oral anticoagulation. Recovery decreased with increasing INR and Beriplex P/N dose. The patients were of median age 70 years (range 22-85) and received a single intravenous dose of 25-50 IU/kg of Beriplex P/N depending on their INR.

Beriplex P/N is distributed and metabolised in the same way as the endogenous coagulation factors II, VII, IX and X.

CLINICAL TRIALS

A phase III, uncontrolled study was undertaken to provide pivotal efficacy and safety data for Beriplex P/N in the reversal of coagulopathy in subjects treated with anticoagulants who required immediate correction of their International Normalised Ratio (INR) due to emergency surgery or acute bleeding. The primary objective was to demonstrate reduction in INR to $\leq$ 1.3 (normalisation) within 30 minutes after the end of the Beriplex P/N infusion. Secondary efficacy variables included the haemostatic efficacy assessment by the investigator and examination of the increase in plasma levels of the coagulation factors.

Forty–three subjects (22 female, 21 male; median age 70, range 22-85) were allocated to three dose groups based on their baseline INR; subjects with INR 2–3.9, 4-6 and > 6 receiving 25, 35 and 50 IU of FIX/kg respectively. Thirty-eight of the 43 subjects received Vitamin K concomitantly at doses ranging from 5 mg to 20 mg (most at 10 mg). Forty of the 43 subjects achieved INR of $\leq$ 1.3; the remaining three subjects had an INR of 1.4 (clinically sufficient to start surgery or stop an acute bleed). The efficacy across groups indicated that a dose based on initial INR is effective. Haemostatic efficacy was classified as very good or satisfactory in 42 subjects (98%). The single infusion of Beriplex P/N led to median maximal levels near-normal for factors II and X and Protein C. There was considerable variability. Recovery decreased with increasing INR.

The efficacy of Beriplex P/N was also established through three supportive trials. The Preston trial (n=42) used the same dose schedule in a similar population requiring urgent reversal of anticoagulant. All subjects received intravenous vitamin K. The target INR of < 1.3 was achieved in 33 patients (79%) within 20 minutes of Beriplex P/N. The other

patients achieved INRs of 1.3-1.9. Trial BE1116/7D-201KO (n=30) used a Beriplex P/N dose of 1,000 IU with another 500 IU if necessary in an acquired deficiency population of whom 22 had severe liver disease and 8 were on anticoagulants. Efficacy was assessed by the physician as very good in 80% and satisfactory in the remainder. After a second dose (n=7), efficacy was very good in 71% and satisfactory in 29%. The Evans trial in 10 subjects requiring urgent reversal of anticoagulation used a Beriplex P/N dose of 30 IU/kg with 5 mg IV vitamin K. Cessation of bleeding occurred within 8 h of treatment in all subjects.

INDICATIONS

Treatment and perioperative prophylaxis of bleedings 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.

CONTRAINDICATIONS

Known hypersensitivity to any of the components of the product.

Risk of thrombosis, angina pectoris, recent myocardial infarction (exception: life-threatening haemorrhages following overdosage of oral anticoagulants, and before induction of a fibrinolytic therapy).

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 (HIT).

PRECAUTIONS

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K dependent coagulation factors (e.g. as induced by treatment of vitamin K antagonists), 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 receiving a vitamin K antagonist may have an underlying hypercoagulable state and infusion of human prothrombin complex may exacerbate this.

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

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

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 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 the case of complex coagulation disorders, such as disseminated intravascular coagulation (DIC) or hyperfibrinolysis, a treatment administering appropriate products (e.g. heparin, antithrombin III, fresh frozen plasma, antifibrinolytics) 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 normalisation of the antithrombin III level).

When Beriplex P/N is used to reverse anticoagulation, resumption of anticoagulation based on the indication should be considered in a timely manner.

Beriplex P/N contains up to 343 mg sodium (approximately 15 mmol) per 100 mL and this is to be taken into consideration by patients on a controlled sodium diet.

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

Pathogen safety

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

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B and hepatitis C viruses (HBV and HCV).

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A (HAV) and parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

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

Effects on fertility
The effects of Beriplex P/N on fertility are unknown.

Use in pregnancy
The safety of Beriplex P/N during pregnancy has not been established. Beriplex P/N should only be used in pregnancy, if clearly indicated. .

Use in lactation
The safety of Beriplex P/N during lactation has not been established..

Paediatric use
The use of Beriplex P/N in the paediatric population has not been established in clinical studies. No data are available regarding the use of Beriplex P/N in case of perinatal bleeding due to vitamin K deficiency in neonates.

Use in the elderly
The use of Beriplex P/N in elderly people (> 65 years) has been demonstrated in clinical studies.

Carcinogenicity
The carcinogenic potential of Beriplex P/N has not been assessed.

Genotoxicity
The genotoxic potential of Beriplex P/N has not been assessed.

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

Effects on laboratory tests
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.

ADVERSE EFFECTS

The following adverse reactions are based on post marketing experience as well as scientific literature. The following standard categories of frequency are used:

Very common:	≥	1/10
Common:	≥	1/100 and <1/10
Uncommon:	≥	1/1,000 and <1/100
Rare:	≥	1/10,000 and <1/1,000
Very rare:	<	1/10,000 (including reported single cases)

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

Vascular disorders:
There is a risk of thromboembolic episodes following the administration of human prothrombin complex, such as pulmonary embolism, thrombotic stroke, portal vein thrombosis, acute myocardial infarction, disseminated intravascular coagulation.

General disorders and administration site conditions:
Increase in body temperature is observed in very rare cases.

Immune system disorders:
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, angina pectoris, tingling, vomiting or wheezing) have been observed very rarely in patients treated with factor IX containing products. In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors.

If allergic-anaphylactic reactions occur, the administration of Beriplex P/N should be discontinued immediately (e.g. discontinue injection) and an appropriate treatment initiated.

Development of antibodies to one or several factors of the prothrombin complex may occur in very rare cases. If such inhibitors occur, the condition will manifest itself as a poor clinical response. In such cases, it is recommended to contact a specialised haemophilia centre.

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).

DOSAGE AND ADMINISTRATION

Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-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), 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).

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

There is no experience in children.

Treatment and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.
The dose will depend on the INR before treatment and the targeted INR. In the following table approximate doses (mL/kg body weight of the reconstituted product and IU factor IX/kg body weight) 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 body weight	1	1.4	2
Approximate dose IU (Factor IX)/kg body weight	25	35	50

It is recommended that the maximum single dose should not exceed 5000 IU 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.

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.

Method of administration
Beriplex P/N should be reconstituted according to the instructions provided. The reconstituted solution should be administered intravenously (not more than 3 IU/kg body weight/min, max. 210 IU/min, approximately 8 mL/min).

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

General instructions
The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discolouration prior to administration. Do not use solutions that are cloudy or have deposits.

Reconstitution and withdrawal must be carried out under aseptic conditions.

Reconstitution
Bring the diluent to room temperature. Ensure that product and diluent vial flip caps are removed and the stoppers are treated with a disinfectant solution and allowed to dry prior to opening the Mix2Vial™ package.

1. Open the Mix2Vial package by peeling away the lid.
2. Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the package and push the blue end straight down through the diluent stopper.
3. Carefully remove the package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set.
4. Place the product vial on an even and firm surface. Invert the diluent vial with the Mix2Vial set attached and push the transparent adapter straight down through the product vial stopper. The diluent will automatically flow into the product vial.
5. With one hand hold the product-side of the Mix2Vial set, hold the diluent-side with the other hand and unscrew the set into two pieces. Discard the diluent vial with the blue part attached.
6. Gently swirl the product vial 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. Inject air into the product vial.

Withdrawal and application
8. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.
9. Now that the concentrate has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the Mix2Vial set from the syringe.

Care must be taken 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 by a separate infusion line.

CAUTION: The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after reconstitution. Any unused solution should be discarded appropriately. Use in one patient on one occasion only. If clots or a gel form, do not use the product.

OVERDOSAGE

To avoid overdosage, regular monitoring of the coagulation status is indicated during the treatment as the use of high doses of prothrombin complex concentrate (overdosage) has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. In case of overdosage the risk of thromboembolic complications or disseminated intravascular coagulation is enhanced in patients at risk of these complications.

PRESENTATION AND STORAGE CONDITIONS

Beriplex P/N 250 is available in vials containing 250 IU of factor IX. Each single pack contains one vial of product, one 10 mL vial of Water for Injections and one Mix2Vial filter transfer device 20/20.

Beriplex P/N 500 is available in vials containing 500 IU of factor IX. Each single pack contains one vial of product, one 20 mL vial of Water for Injections and one Mix2Vial filter transfer device 20/20.

The physico-chemical stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (max. 25°C). However, to reduce microbiological hazard, the product should be used as soon as practicable after reconstitution. If storage is necessary, hold at room temperature (max. 25°C) for not more than 6 hours.

Store below 25°C. Do not freeze. Keep the vial in the outer carton, in order to protect from light. Do not use after the expiry date.

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POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF APPROVAL

Therapeutic Goods Administration approval: 15 January 2010

Beriplex™ is a trademark of the CSL Group
Mix2Vial™ is a trademark of Medimop Medical Projects Ltd

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