AUSTRALIAN PRODUCT INFORMATION

Beriplex® P/N

(Human prothrombin complex)

1 NAME OF THE MEDICINE

Human prothrombin complex

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Beriplex® P/N is presented as a powder, containing human prothrombin complex, in packs of 250 IU, 500 IU and 1000 IU factor IX, for reconstitution with a vial of diluent.

P/N refers to the virus inactivation and removal steps of pasteurisation and nanofiltration (virus filtration).

The product contains the following IU of the human coagulation factors in **Table 1.**

Table 1: Active ingredient composition

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)	Beriplex® P/N 1000 content per vial (IU)
Active ingredients				
Human coagulation factor II	20–48	200–480	400–960	800–1920
Human coagulation factor VII	10–25	100–250	200–500	400–1000
Human coagulation factor IX	20–31	200–310	400–620	800–1240
Human coagulation factor X	22–60	220–600	440–1200	880–2400
Other active ingredients				
Protein C	15–45	150–450	300–900	600–1800
Protein S	12–38	120–380	240–760	480–1520

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.

Beriplex® P/N contains up to 343 mg sodium (approximately 15 mmol) and up to 200 IU heparin per 100 mL reconstituted solution.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection

Powder: white or slightly coloured powder or friable solid

Diluent (Water for Injections): clear, colourless.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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 (e.g. International Normalised Ratio (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.

Bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment

The dose will depend on the INR before treatment and the targeted INR. The pre-treatment INR should be measured as close as possible to the time of dosing in order to calculate the appropriate dose of Beriplex® P/N. In **Table 2**, 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.

Table 2: Dose calculation

Pre-treatment 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

Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg the maximum single dose (IU of factor IX) should therefore not exceed 2500 IU for an INR of 2.0–3.9, 3500 IU for an INR of 4.0–6.0 and 5000 IU for an INR of >6.0.

The correction of the vitamin K antagonist-induced impairment of haemostasis is commonly reached approximately 30 minutes after the injection. The simultaneous administration of vitamin K should be considered in patients receiving Beriplex® P/N for urgent reversal of vitamin K antagonists since vitamin K usually takes effect within 4–6 hours. Repeated dosing with Beriplex® P/N for patients requiring urgent reversal of vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.

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.

Administration

Beriplex® P/N should be reconstituted according to the instructions provided. The reconstituted solution should be administered by a separate injection/infusion line by slow

intravenous injection, at a rate not exceeding 3 IU/kg body weight/minute, max. 210 IU/minute, approximately 8 mL/minute.

Whilst the physico-chemical stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (max. 25°C), Beriplex® P/N contains no antimicrobial preservative. Therefore, it is recommended that the product should be used immediately after reconstitution. Use in one patient on one occasion only. Any unused solution should be discarded appropriately. If a clot or a gel forms, do not use the product.

General instructions

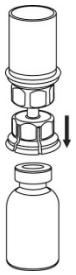
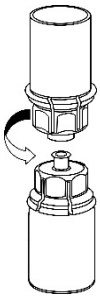
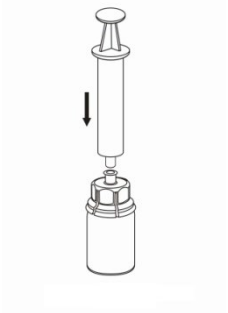
The solution should be clear or slightly opalescent. After filtering/withdrawal reconstituted product should be inspected visually for particulate matter and discolouration prior to administration. Do not use solutions that are cloudy or have deposits.

Reconstitution and withdrawal must be carried out under aseptic conditions.

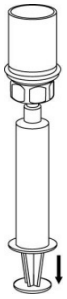
Reconstitution

Bring the diluent to room temperature. Ensure 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	1. Open the Mix2Vial™ package by peeling off the lid. Do **not** remove the Mix2Vial™ from the blister package.
 2	2. Place the **diluent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial™ together with the blister package and push the spike of the **blue** adapter end **straight down** through the diluent vial stopper.

 3	3. Carefully remove the blister package from the Mix2Vial™ set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial™ set.
 4	4. Place the **product vial** on an even and firm surface. Invert the diluent vial with the Mix2Vial™ set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The diluent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial™ set, and with the other hand grasp the diluent-side and carefully unscrew the set anticlockwise into two pieces. Discard the diluent vial with the blue Mix2Vial™ attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial™'s Luer lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial™ adapter from the syringe by unscrewing anticlockwise.

Care should 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 could therefore be administered to the patient.

In case more than one vial of Beriplex® P/N is required, it is possible to pool several vials of Beriplex® P/N for a single infusion via a commercially available infusion device.

The Beriplex® P/N solution must not be diluted.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

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). Beriplex® P/N contains heparin.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General precautions

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

In patients with acquired deficiency of vitamin K dependent coagulation factors (e.g. as induced by treatment with 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.

Hypersensitivity reactions

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.

Thromboembolic risk

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 peri- or postoperatively, to neonates or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency. In each of these situations, the potential benefit of treatment with Beriplex® P/N should be weighed against the potential risk of such complications.

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

Disseminated Intravascular Coagulation (DIC)

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). Beriplex® P/N was not studied in patients with complex coagulation disorders such as DIC or hyperfibrinolysis.

Resumption of anticoagulation

Reversing vitamin K antagonists exposes patients to the risk of the underlying disease. Resumption of anticoagulation should be carefully considered as soon as possible.

Heparin-Induced Thrombocytopenia type II

Undesirable reactions may include the development of HIT type II. Characteristic signs of HIT are a platelet count drop >50% 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).

Other

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

Beriplex® P/N 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.

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. In addition, the Beriplex® P/N manufacturing process includes pasteurisation (60°C for 10 hours) and nanofiltration as dedicated virus inactivation and removal steps to reduce the possibility of virus transmission.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and for the non-enveloped virus hepatitis A (HAV) and parvovirus B19.

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.

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

It is strongly recommended that every time that Beriplex® P/N is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Use in the elderly

The safety and efficacy of Beriplex® P/N in elderly people (>65 years) has been demonstrated in clinical studies.

Paediatric use

The safety and efficacy of Beriplex® P/N in the paediatric population has not been established in clinical studies.

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy

The safety of human prothrombin complex during pregnancy has not been established. Animal studies to assess effects on embryofoetal development have not been conducted because there is no evidence that clotting factors cross the placental barrier.

Human prothrombin complex should only be used in pregnancy if clearly indicated.

Use in lactation

The safety of human prothrombin complex during lactation has not been established.

Human prothrombin complex should only be used in lactation if clearly indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial experience

Adverse events reported for Beriplex® P/N and plasma during the acute major bleeding and urgent surgery/invasive procedures Randomised Controlled Trials (RCTs) are summarised in **Table 3**. Both RCTs were prospective, randomised, open-label, active-controlled multicentre non-inferiority trials. The acute major bleeding trial enrolled a total of 212 subjects (103 treated with Beriplex® P/N and 109 with plasma) that were aged from 26 years to 96 years. The urgent surgery/invasive procedures trial enrolled a total of 176 subjects (88 treated with Beriplex® P/N and 88 with plasma) that were aged from 27 years to 94 years.

Table 3: Adverse events reported in more than 5 Subjects (≥2.8%) following Beriplex® P/N or plasma administration in RCTs[a, b]

System Organ Class	No. (%) of subjects	
	Beriplex® P/N (N = 191)	Plasma (N = 197)
Nervous system disorders		
Headache	14 (7.3%)	7 (3.6%)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	8 (4.2%)	3 (1.5%)
Respiratory distress/dyspnea/hypoxia	7 (3.7%)	10 (5.1%)
Pulmonary oedema[c]	3 (1.6%)	10 (5.1%)
Gastrointestinal disorders		
Nausea/vomiting	12 (6.3%)	8 (4.1%)
Diarrhoea	4 (2.1%)	7 (3.6%)
Cardiac disorders		
Tachycardia	9 (4.7%)	2 (1.0%)
Atrial fibrillation	8 (4.2%)	6 (3.0%)
Metabolism and nutrition disorders		
Fluid overload[d]	5 (2.6%)	16 (8.1%)
Hypokalemia	9 (4.7%)	14 (7.1%)
Psychiatric disorders		
Insomnia	9 (4.7%)	6 (3.0%)
Vascular disorders		
Hypotension[e]	14 (7.3%)	10 (5.1%)
Injury, poisoning and procedural complications		
Skin laceration/contusion/subcutaneous haematoma	8 (4.2%)	5 (2.5%)
Blood and lymphatic system disorders		
Anaemia[f]	11 (5.8%)	16 (8.1%)

Note:

[a] Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

[b] In this table adverse events are included that began during or within 72 hours of test product infusion plus adverse events considered possibly/probably related or related to study treatment according to the investigator, sponsor, or the blinded safety adjudication board (SAB), and with at least a 1.3-fold difference between treatments.

[c] One patient experienced both an event of pulmonary oedema as well as an event of fluid overload (cardiac failure). Since these two types of events were separated in the table, this subject was counted twice.

[d] Includes fluid overload and cardiac failure congestive.

[e] Includes orthostatic hypotension, hypotension, and haemorrhagic shock.

[f] Includes anaemia, haemoglobin decreased, and haematocrit decreased.

Thromboembolic events

In RCTs, there were 13 subjects (6.8%) in the Beriplex® P/N group who experienced possible thromboembolic events (TEEs) and 14 (7.1%) who had TEEs in the plasma group. When also considering the events which began during or within 72 hours of test product infusion, the incidence was 9 (4.7%) in the Beriplex® P/N group and 8 (4.1%) in the plasma group.

Table 4: Thromboembolic events and unknown cause of death following Beriplex® P/N or plasma administration in RCTs

System Organ Class	No. (%) of subjects			
	Acute major bleeding study		Urgent surgery/invasive procedures study	
	Beriplex® P/N (N = 103)	Plasma (N = 109)	Beriplex® P/N (N = 88)	Plasma (N = 88)
Any possible TEE[a]	**9 (8.7%)**	**6 (5.5%)**	**4 (4.5)**	**8 (9.1)**
TEE Adverse reactions	**6 (5.5%)**	**4 (3.7%)**	**4 (4.5)**	**4 (4.5)**
Cardiac disorders				
Myocardial infarction	0	1 (0.9%)	0	2 (2.3)
Myocardial ischaemia	0	2 (1.8%)	0	0
Nervous system disorders				
Ischaemic cerebrovascular accident (stroke)	2 (1.9%)	0	1 (1.1)	0
Embolic cerebral infarction	0	0	0	1 (1.1)
Cerebrovascular disorder	0	1 (0.9%)	0	0
Vascular disorders				
Venous thrombosis calf	1 (1.0%)	0	0	0
Venous thrombosis radial vein	0	0	1 (1.1)	0
Thrombosis (microthrombosis of toes)	0	0	1 (1.1)	0
Deep vein thrombosis (DVT)	1 (1.0%)	0	1 (1.1)	1 (1.1)
Fistula clot	1 (1.0%)	0	0	0
Unknown cause of death (not confirmed TEE)				
Sudden death	1 (1.0%)	0	0	0

[a] The tabulation of possible TEEs includes subjects with confirmed TEEs as well as 3 subjects in the acute major bleeding RCT Beriplex® P/N group that died of unknown causes on days 7, 31, and 38 and 1 subject in the urgent surgery/invasive procedures RCT plasma group that died of unknown causes on day 18. The death on day 7 was considered possibly related to study product by the SAB and is tabulated as an adverse reaction.

Summary of the safety profile – adverse drug reactions

Adverse events from clinical trial data, post-marketing experience as well as scientific literature were analysed for determining causal relationship to Beriplex® P/N. The resulting adverse reactions are summarised in this section.

Allergic or anaphylactic-type reactions have been uncommonly observed, including severe anaphylactic reactions. See Section 4.4 Special warnings and precautions for use.

Replacement therapy may lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. In such cases, it is recommended to contact a specialised haemophilia centre for guidance.

Anaphylactic reactions have been observed in patients with antibodies to factors contained in Beriplex® P/N.

Increase in body temperature has been commonly observed.

There is a risk of thromboembolic episodes following the administration of human prothrombin complex. See Section 4.4 Special warnings and precautions for use.

Adverse reactions in **Table 5** are classified according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been based on clinical trial data, according to the following convention: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1000 and <1/100); rare (≥1/10,000 and <1/1000); very rare (<1/10,000) or not known (cannot be estimated from the available data).

Table 5: Frequency of adverse reactions

MedDRA Standard System Organ Class	Adverse Drug Reaction by Preferred Term	Frequency
Vascular disorders and other System Organ Classes	Thromboembolic events[a] (arterial and venous)	Common
Blood and lymphatic system disorders	Disseminated intravascular coagulation	Not known
Immune system disorders	Hypersensitivity or allergic reactions	Uncommon
	Anaphylactic reactions including anaphylactic shock	Not known
Nervous system disorders	Headache	Common
General disorders and administration site conditions	Body temperature increased	Common

[a] Including cases with fatal outcome.

Adverse reactions only observed in post-marketing experience included disseminated intravascular coagulation, anaphylactic reactions including anaphylactic shock and development of antibodies. For these adverse reactions no frequency category can be determined.

For safety with respect to transmissible agents, see Pathogen safety in Section 4.4 Special warnings and precautions for use.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or the National Poisons Centre on 0800 POISON (0800 764766) (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors II, VII, IX and X in combination.

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.

Clinical trials

Beriplex® P/N has been evaluated in three pivotal Phase III studies to determine the efficacy, safety and tolerability of Beriplex® P/N in subjects with acquired deficiency of prothrombin complex coagulation factors. The three studies evaluated the efficacy, safety and tolerability of Beriplex® P/N in subjects who had undergone vitamin K antagonist (VKA) therapy and who required urgent replacement of their vitamin K dependent clotting factors to treat acute major bleeding or to prepare for an urgent surgery/invasive procedure. The results of these studies demonstrate that replacement of vitamin K dependent clotting factors with Beriplex® P/N (i) effectively reverses the effect of oral anticoagulation by rapidly decreasing the INR, (ii) achieves haemostatic efficiency comparable to plasma and (iii) decreases the INR more rapidly than plasma in subjects who have been treated with oral VKA and who required urgent replacement of their vitamin K dependent clotting factors.

Acute Major Bleeding Study

The acute major bleeding Phase IIIb study was a prospective, open-labelled, non-inferiority multicentre trial using plasma as active control. The primary objective was to compare the haemostatic efficacy of Beriplex® P/N and plasma over the first 24 hours following infusion. Efficacy was determined by a blinded independent board. Criteria for effective haemostasis were based upon standard clinical assessments including vital signs, haemoglobin measurements, and computed tomography assessments at pre-defined time points, as relevant to the type of bleeding. A co-primary objective was to compare the efficacy of Beriplex® P/N and plasma in reducing the INR to ≤1.3 (normalisation) at 30 minutes after the end of infusion.

The modified efficacy population comprised 202 subjects (101 female and 101 male; mean age 69.8, range 29–96 in the Beriplex® P/N treated group and mean age 69.8, range 26–92 for the plasma treated group) with a baseline INR >1.3 and recent use of a VKA anticoagulant.

These were randomised to a single dose of Beriplex® P/N (98 subjects) or plasma (104 subjects). The subjects were allocated to three dose groups according to their baseline INR. In the Beriplex® P/N treated group, subjects with INR 2 to <4, 4 to 6 or >6 received 25, 35 or 50 IU of factor X/kg, respectively. In the plasma treated group, subjects with INR 2 to <4, 4 to 6 or >6 received 10, 12 or 15 mL of plasma/kg, respectively. Intravenous vitamin K was administered concomitantly.

Haemostatic efficacy was classified as excellent or good (i.e. effective) in 71 subjects (72.4%, 95% CI [63.6; 81.3]) in the Beriplex® P/N treated group and 68 subjects (65.4%) in the plasma treated group. The difference between groups was 7.1% in favour of Beriplex® P/N, and the lower limit of the 95% CI was -5.8%. Analysis of the treatment difference confirmed the non-inferiority of Beriplex® P/N treatment compared to plasma treatment (lower limit of 95% CI was >-10%), but did not demonstrate superiority (lower limit of 95% CI was not >0). For the co-primary endpoint, there was a rapid reduction in INR in 61 subjects (62.2%) in the Beriplex® P/N group and 10 subjects (9.6%) in the plasma group. The difference between the groups was 52.6%. The lower limit of the 95% confidence interval (CI) of 31.9% demonstrated superiority of Beriplex® P/N versus plasma for this endpoint.

Urgent Surgery/Invasive Procedure Study

This Phase IIIb study was a prospective, open-label, non-inferiority, multicentre clinical trial using plasma as active control. The primary efficacy objective was haemostatic efficacy over the time period from the start of infusion of Beriplex® P/N or plasma until the end of the urgent surgery/invasive procedure. Criteria for effective haemostasis were based upon the difference between predicted and actual blood losses, subjective haemostasis rating, and the need for additional blood products containing coagulation factors. A co-primary objective was to compare the efficacy of Beriplex® P/N and plasma in reducing the preoperative INR values to ≤1.3 at 30 minutes after the end of the infusion.

The modified efficacy population comprised 168 subjects (68 female and 100 male; mean age 69.4, range 32–94 in the Beriplex® P/N treated group and mean age 66.0, range 27–90 for the plasma treated group) with a baseline INR >1.3 and recent use of a VKA anticoagulant. Eighty-seven of these were randomised to receive a single dose of Beriplex® P/N; 81 were randomised to receive a single dose of plasma. The subjects were allocated to one of three dose groups according to their baseline INR. In the Beriplex® P/N treated group, subjects with INR 2 to <4, 4 to 6 or >6 received 25, 35 or 50 IU of factor IX/kg, respectively. In the plasma treated group, subjects with INR 2 to <4, 4 to 6 or >6 received 10, 12 or 15 mL of plasma/kg, respectively. Intravenous or oral vitamin K was administered concomitantly.

Haemostatic efficacy was classified as excellent or good (i.e. effective) in 78 subjects (89.7% with a 95% CI [83.3; 96.1]) in the Beriplex® P/N group and 61 subjects (75.3% with a 95%

CI [65.9; 84.7]) in the plasma group. The difference between groups was 14.3% in favour of Beriplex® P/N and the lower limit of the 95% CI was 2.8%. Analysis of the treatment difference confirmed the non-inferiority (lower limit of 95% CI was >-10%) and the superiority (lower limit of 95% CI was >0) of Beriplex® P/N compared to plasma. For the co-primary objective, there was a rapid reduction in INR in 48 subjects (55.2%) in the Beriplex® P/N group and 8 subjects (9.9%) in the plasma group. The difference between the groups was 45.3%. The lower limit of the 95% CI of 31.9% demonstrated superiority of Beriplex® P/N versus plasma for this endpoint.

European Bleeding and Surgical Study

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 INR due to emergency surgery or acute bleeding. The primary objective was to demonstrate reduction in INR to ≤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. Vitamin K was administered concomitantly to 38 of the 43 subjects at doses ranging from 5 mg to 20 mg (most at 10 mg).

Forty of the 43 subjects achieved INR of ≤1.3; the remaining three subjects had an INR of 1.4 (clinically sufficient to start surgery or enable normal coagulation). 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%). Levels of coagulation factors II, VII, IX, X, protein C and protein S were measured after the infusion of Beriplex® P/N or plasma. Results were similar for subjects with acute major bleeding or subjects requiring an urgent surgery or invasive procedure. The single infusion of Beriplex® P/N led to a direct increase of all component plasma levels, reaching normal or near normal median values for factors II and X and protein C within 30 minutes. Levels of some factors continued to increase at later time points, consistent with the effect of concomitant vitamin K treatment.

Other Studies

The efficacy of Beriplex® P/N was also assessed in three supportive trials. The first two studies enrolled patients requiring urgent reversal of an acquired deficiency of the vitamin K dependent coagulation factors. In the first study, 33 subjects (79%) achieved an INR of <1.3 and eight subjects (21%) achieved an INR 1.3–1.9 within 20 minutes of Beriplex® P/N administration. In the second acquired deficiency study, clinical efficacy was assessed by the

physician's judgement concerning the adequacy of stopping an ongoing bleeding or avoidance of excessive bleeding during a surgical intervention. Clinical efficacy was assessed as very good in 80% of subjects and satisfactory in the remaining subjects, following a Beriplex® P/N dose of 1000 IU. After a second dose of Beriplex® P/N (n = 7), efficacy was very good in 71% of subjects and satisfactory in 29% of subjects. In the third study, subjects requiring urgent reversal of over anticoagulation (INR >8.0) were administered a Beriplex® P/N dose of 30 IU/kg with 5 mg intravenous vitamin K. Cessation of bleeding occurred within 8 hours of treatment in all 10 subjects.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic and *in vivo* recovery (IVR) data were generated in a healthy volunteer study (n = 15) and in two studies in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleedings (n = 98, n = 43).

Healthy volunteer study

Fifteen healthy volunteers were administered 50 IU/kg of Beriplex® P/N. The IVR is the increase in measurable factor levels in plasma (IU/mL) that may be expected following an infusion of factors (IU/kg) administered as a dose of Beriplex® P/N. Incremental IVRs for factors II, VII, IX, X and protein C and protein S were assessed. All maximum component levels occurred within the 3 hour time interval. Mean incremental IVRs ranged between 0.016 IU/mL for factor IX and 0.028 IU/mL for protein C. Median plasma half-lives and incremental IVRs are indicated in **Table 6**.

Table 6: Active ingredient pharmacokinetic properties

Parameter	Median plasma half-lives hours (range)	Incremental IVR (IU/mL per IU/kg body weight)	
		Geometric mean	90% CI[b]
Factor II	60 (25–135)	0.022	(0.020–0.023)
Factor VII	4 (2–9)	0.024	(0.023–0.026)
Factor IX	17 (10–127)[a]	0.016	(0.014–0.018)
Factor X	31 (17–44)	0.021	(0.020–0.023)
Protein C	47 (9–122)[a]	0.028	(0.027–0.030)
Protein S	49 (33–83)[a]	0.020	(0.018–0.021)

[a] Terminal half-life; two-compartment-model.

[b] Confidence interval.

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

Intravenous administration means that the preparation is available immediately; bioavailability is equivalent to the dose administered.

Study in reversal of vitamin K antagonist treatment for acute major bleeding

The mean IVR was calculated in 98 subjects who received Beriplex® P/N for treatment of bleeding during vitamin K antagonist treatment. Doses of Beriplex® P/N administered were 25, 35 or 50 IU of factor IX/kg depending on the subject's baseline INR. The incremental IVR responses ranged between 0.016 IU/mL for factor VII and 0.019 IU/mL for protein C.

Study in reversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleeding

The mean IVR was calculated in 43 subjects who received Beriplex® P/N for treatment of bleeding or perioperative prophylaxis of bleedings during vitamin K antagonist treatment. The intravenous administration of 1 IU/kg Beriplex® P/N increased plasma levels of the vitamin K dependent coagulation factors ranging from 0.013–0.023 IU/mL.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Heparin sodium (porcine)

Albumin

Antithrombin III

Sodium chloride

Sodium citrate

HCl or NaOH (in small amounts for pH adjustment).

6.2 INCOMPATIBILITIES

Do not mix Beriplex® P/N with other medicinal products; administer through a separate injection/infusion line.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the carton.

Reconstituted product

Whilst the physico-chemical stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (max. 25°C), Beriplex® P/N contains no antimicrobial preservative. Therefore, it is recommended that the product should be used immediately after reconstitution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Beriplex® P/N 250:

- Powder: Injection vial of glass, sealed with rubber infusion stopper, aluminium seal and plastic flip-off cap
- Diluent: 10 mL Water for Injections in an injection vial of glass, sealed with rubber infusion stopper, aluminium seal and plastic flip-off cap
- Device for reconstitution: one Mix2Vial™ filter transfer set 20/20.

Beriplex® P/N 500:

- Powder: Injection vial of glass, sealed with rubber infusion stopper, aluminium seal and plastic flip-off cap
- Diluent: 20 mL Water for Injections in an injection vial of glass, sealed with rubber infusion stopper, aluminium seal and plastic flip-off cap
- Device for reconstitution: one Mix2Vial™ filter transfer set 20/20.

Beriplex® P/N 1000:

- Powder: Injection vial of glass, sealed with rubber infusion stopper, aluminium seal and plastic flip-off cap
- Diluent: 40 mL Water for Injections in an injection vial of glass, sealed with rubber infusion stopper, aluminium seal and plastic flip-off cap
- Device for reconstitution: one Mix2Vial™ filter transfer set 20/20.

Beriplex® P/N is packaged in latex free materials.

Not all registered presentations may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

37224-63-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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05 February 2010

10 DATE OF REVISION

10 January 2022

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	New Zealand contact details for reporting adverse reactions added
4.9	New Zealand contact details for management of overdose added
8	Manufacturer and New Zealand sponsor contact details added
2, 4.2, 4.8, 5.1, 5.2, 6.2, 6.3, 6.5, 8	Minor editorial changes made