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Long-term safety and efficacy of a pasteurized nanofiltrated prothrombin complex concentrate (Beriplex P/N): a pharmacovigilance study

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Editor's key points

- This pharmacovigilance study reports on the long-term safety and efficacy of a pasteurized nanofiltrated prothrombin complex concentrate (Beriplex P/N).
- The reported number of serious adverse events (AEs) recorded in the Beriplex P/N pharmacovigilance database was low.
- A review of published AEs from clinical studies showed no anaphylaxis or allergic reactions, no virus transmission, no cases of HIT type II, and a low incidence of clinically overt thromboembolic complications.

Background. The rapid reversal of the effects of vitamin K antagonists is often required in cases of emergency surgery and life-threatening bleeding, or during bleeding associated with high morbidity and mortality such as intracranial haemorrhage. Increasingly, four-factor prothrombin complex concentrates (PCCs) containing high and well-balanced concentrations of vitamin K-dependent coagulation factors are recommended for emergency oral anticoagulation reversal. Both the safety and efficacy of such products are currently in focus, and their administration is now expanding into the critical care setting for the treatment of life-threatening bleeding and coagulopathy resulting either perioperatively or in cases of acute trauma.

Methods. After 15 yr of clinical use, findings of a pharmacovigilance report (February 1996–March 2012) relating to the four-factor PCC Beriplex P/N (CSL Behring, Marburg, Germany) were analysed and are presented here. Furthermore, a review of the literature with regard to the efficacy and safety of four-factor PCCs was performed.

Results. Since receiving marketing authorization (February 21, 1996), ~647 250 standard applications of Beriplex P/N have taken place. During this time, 21 thromboembolic events judged to be possibly related to Beriplex P/N administration have been reported, while no incidences of viral transmission or heparin-induced thrombocytopenia were documented. The low risk of thromboembolic events reported during the observation period (one in ~31 000) is in line with the incidence observed with other four-factor PCCs.

Conclusions. In general, four-factor PCCs have proven to be well tolerated and highly effective in the rapid reversal of vitamin K antagonists.

Keywords: bleeding; pharmacovigilance; prothrombin; safety; vitamin K antagonist

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Oral anticoagulation therapies such as warfarin are the primary treatment for patients at risk of thrombosis.[1] The highly effective role of vitamin K antagonist administration in the reduction in thromboembolic events has been extensively documented;[2–5] however, the use of these anticoagulants is coupled with an increased risk of bleeding complications.[6–9] The annual risk of gastrointestinal and urinary tract bleeding and also intracranial haemorrhage (ICH) is increased in the anticoagulated population,[9–14] with an annual fatality rate of ~1%.[10 15] The potentially serious nature of these complications means that an effective and rapid treatment for vitamin K antagonist reversal is required.

One therapeutic option for the management of vitamin K antagonist reversal is four-factor prothrombin complex concentrates (PCCs). PCCs contain a combination of the coagulation factors which are inhibited by vitamin K antagonists [factors (F) II, VII, IX, and X, and proteins C, S, and Z).[16] PCC administration with concomitant vitamin K is recommended for facilitating the emergency reversal of oral anticoagulation,[17–20] and has also been used for treating cases of coagulation defects related to liver disease, and also acquired deficiency of vitamin K-dependent coagulation factors in the perioperative setting.[21–23] The combination of an ageing population and thus the increasing number of anticoagulated patients, and also the increasing administration of PCCs across a wider range of indications, means that the efficacy and safety of these products is currently in focus.[24 25] A growing number of studies have shown that PCCs facilitate the rapid and predictable reversal of

vitamin K antagonist therapy in those patients with acute bleeding or requiring emergency surgery.[26–36]

Despite their efficacy, the widespread use of PCCs has been hampered by concerns over their safety.[37] As with all clotting factor concentrates and blood plasma-derived products, thrombogenicity and the potential for pathogen transmission are the primary safety considerations relating to PCC administration.[38–40] To investigate the safety of treatment since its market authorization, an analysis of pharmacovigilance data related to Beriplex P/N (CSL Behring GmbH, Marburg, Germany) administration is presented here for the first time. These data are updated from those previously presented at the 22nd Congress of the International Society of Thrombosis and Haemostasis. Furthermore, included here is a review of recent studies involving commercially available four-factor PCCs, which was undertaken to establish the efficacy and safety profiles of these products across a range of clinical settings.

Methods

Analysis of pharmacovigilance data

Beriplex P/N has been licensed across Europe for a broad range of indications including the reversal of vitamin K antagonist therapy, clotting factor supplementation in severe liver disease, and the treatment of acquired bleeding since February 1996. A retrospective review of the global pharmacovigilance database of CSL Behring between February 1996 and March 2012 was performed [sources: spontaneous reports, case reports from the scientific literature (including published case reports from investigator-initiated clinical trials). and, where applicable, non-interventional post-authorization studies]. Suspected adverse reactions possibly related to Beriplex P/N administration were identified. Information regarding the clinical use of Beriplex P/N including indication and dosage was also collated. Ethical approval was not required for this study.

Review of four-factor PCC efficacy and safety

A literature review was performed to assess the efficacy and safety of commercially available PCCs. Literature searches were performed using the PubMed online search tool;[41] the search terms applied across all search fields were 'prothrombin complex concentrate and safety'; 'prothrombin complex concentrate and efficacy'; 'prothrombin complex concentrate and reversal'; 'prothrombin complex concentrate and thrombosis'; and 'prothrombin complex concentrate and embolism'. Reports of clinical trials reporting adverse events (AEs) between February 1996 and March 2012 were reviewed. Relevant information relating to clinical indication, product efficacy, and AEs related to PCC administration were identified.

Results

Analysis of pharmacovigilance database

A total of 1 294 500 900 IU Beriplex P/N were administered during the observation period. Assuming an average dose of 2000 IU per patient, ~647 250 infusions have been performed to treat a number of indications, including vitamin K antagonist reversal and clotting factor supplementation in liver disease. When considering the primary safety concerns related to allogeneic administration, an analysis of the safety review showed that there were no reports of either viral transmission or heparin-induced thrombocytopenia (HIT) type II related to Beriplex P/N administration (Table 1).

A total of 21 cases of suspected thromboembolic events were recorded (Table 2)[33 42–46] of these, 13 occurred in patients receiving Beriplex P/N for anticoagulant reversal. An analysis of these events revealed that pre-existing or concomitant conditions likely to result in thromboembolism were present in all patients.

Within the context of total infusions performed, a ratio of 1 thromboembolic event per ~31 000 infusions was reported.

Review of four-factor PCC safety and efficacy

A review of the literature demonstrated the efficacy and safety profiles of several four-factor PCCs. Their use for the reversal of vitamin K antagonist therapy, the supplementation of coagulation factors in liver disease, and the treatment of trauma-related bleeding was evaluated. A summary of nine prospective studies is shown in Table 3;[22 27 29 32–35 43 47 48] any incidences of serious AEs were recorded, with cases of viral transmission or thromboembolic events being highlighted. Four cases of thrombotic events were reported in the studies identified;[30–32 47] of these, two were with Beriplex P/N and are also captured in the analysis of pharmacovigilance data above (Table 2). There were three cases of seroconversion for parvovirus B19 reported after the use of Octaplex® (Octapharma, Lachen, Switzerland).[29 34]

An additional three thromboembolic events (cerebral infarction, pulmonary embolism, and an embolism of a brachial artery) which were potentially associated with PCC administration were described in a retrospective pilot study of patients undergoing aortic arch replacement after acute type A aortic dissection.[49] All patients in this study underwent prolonged cardiopulmonary bypass including isolated head perfusion and a phase with deep hypothermic

Table 1 Pharmacovigilance data recorded for the period February 1996 to March 2012. Pharmacovigilance database is maintained by CSL Behring, Marburg, Germany. *Possibly related to Beriplex P/N (sources: spontaneous report and case reports from the scientific literature, non-interventional post-authorization studies)

	Beriplex P/N
Marketing authorization	February 21, 1996
Amount manufactured (IU)	1 294 500 970
Estimated standard applications	~647 250
Suspected virus transmissions*	0
Suspected cases of HIT type II	0
Suspected cases of thromboembolic events*	21

Table 2 Summary of 21 cases of suspected (possibly related) thromboembolic events occurring after Beriplex P/N administration. CT, computed tomography; INR, international normalized ratio; IU, international unit; PCC, prothrombin complex concentrate

Case, gender, age (yr)	Reason for Beriplex P/N administration	Presentation
Case 1, male, age unknown Case report from the scientific literature; Preston and colleagues[33] (Table 3)	In an investigator-initiated interventional study (rapid reversal of oral anticoagulation with warfarin by a PCC), emergency anticoagulation reversal was carried out using Beriplex P/N (dose unknown) to allow leg amputation. Patient had received oral anticoagulants for treatment of severe peripheral atherosclerotic disease	Patient died from thrombotic stroke after leg amputation 48 h after receiving Beriplex P/N
Case 2, male, 25 Case report from the scientific literature; Sakka and colleagues[44]	Patient with trisomy 21 and atrioventricular canal defect (AV septal defect) was admitted for laparoscopy due to suspicion of acute appendicitis. Beriplex P/N 3000 IU was administered for correction of a coagulopathy	After operation, the patient developed intestine infarction, disseminated intravascular coagulation, and multi-organ failure
Case 3, male, 77	Beriplex P/N 30 IU kg^{-1} (bodyweight unknown) was administered for reversal of oral anticoagulation coagulopathy in a patient presenting with severe fractured pelvis, tibia, and fibula after a road traffic accident	After being stable for ~12 h, the patient subsequently developed massive blood loss and disseminated intravascular coagulopathy
Case 4, male, 70 Pabinger and colleagues[31] (see also Table 3)	A 70-yr-old male patient with metastatic gastrointestinal cancer and arrhythmia absoluta was treated with marketed Beriplex P/N 1500 IU during a clinical study. The patient had already received the study drug (also Beriplex P/N) when he was in need of a second infusion of PCC, and was thus treated with a marketed batch of Beriplex P/N (not study drug)	The patient experienced shortness of breath and died 4 days later. Cause of death was suspected to be pulmonary embolism
Case 5, male, 52 Case report from the scientific literature; Bagot and colleagues[42]	Beriplex P/N was administered (500 IU) for reversal of oral anticoagulation coagulopathy before surgery to treat a perforated bowel diverticulum with abdominal sepsis	Immediately before wound closure, the patient sustained a fatal cardiorespiratory arrest. Post-mortem examination revealed acute myocardial infarction with moderate atherosclerosis of all coronary vessels. A causal relationship could not be excluded
Case 6, male, 65 Case report from the scientific literature; White and colleagues[46]	A patient receiving oral anticoagulation after cardiac surgery, presented 4 weeks later with abdominal pain. Although gastrointestinal bleeding was excluded, the patient received Beriplex P/N 4000 IU PCC and vitamin K to reverse the effects of warfarin	After CT, cardiac surgery revealed a heart entirely encaged in an organized thrombus which was manually evacuated. The patient made a full recovery. In this case, inappropriate use of Beriplex P/N (in the absence of haemorrhage) most likely caused clotting of a sero-sanguinous pericardial effusion
Case 7, female, 67	Beriplex P/N was administered (4000 IU) for reversal of oral anticoagulation coagulopathy before emergency surgery	The patient developed thrombosis of the left leg and fulminant pulmonary embolism
Case 8, male, 67	Beriplex P/N was administered (3000 IU) for reversal of oral anticoagulation coagulopathy before emergency surgery	The patient developed a fatal fulminant pulmonary embolism
Case 9, male, 70	Beriplex P/N (1500 IU) was given to stop postoperative bleeding (INR >8) after an emergency femoral embolectomy for acute leg ischaemia	Two hours after administration of Beriplex P/N, the patient developed a thrombosed graft/arterial thrombosus. INR was 1.4. The patient had a medical history of venous thromboembolism, peripheral vascular disease, warfarin therapy, lung cancer, and liver metastasis
Case 10, female, 85 Case report from the scientific literature	Beriplex P/N 1000 IU was given for haematuria. INR before administration of Beriplex P/N was 2.2	Patient had a medical history of arterial fibrillation and prosthetic heart valve and was on vitamin K antagonist therapy. Within 1 week of treatment with Beriplex P/N, the patient experienced myocardial infarction
Case 11, male, 84	Beriplex P/N 250 IU was administered for reversal of warfarin (INR=4)	Patient experienced myocardial infarction 10 min after administration of Beriplex P/N. Patient had a medical history of ischaemic heart disease and atrial fibrillation

Continued

Table 2 *Continued*

Case, gender, age (yr)	Reason for Beriplex P/N administration	Presentation
Case 12, gender and age unknown Case report from the scientific literature; Weiss and colleagues[45]	Patient received 3000 IU PCC (brand not specified) for massive bleeding during heart surgery	Patient developed myocardial infarction on the first postoperative day. Additional pro-coagulators such as fibrinogen and FFP were also administered
Case 13, male, 63	Patient received Beriplex P/N 3000 IU for warfarin reversal and gastrointestinal bleeding. INR before administration was >9	One day after administration of Beriplex P/N, the patient developed an acute/subacute left posterior cerebral artery territory infarct. The patient had a medical history of coronary artery disease, myocardial infarction, coronary artery bypass, diabetes type II, cerebrovascular accident/transient ischaemic attack, thromboembolic events, and carcinoma
Case 14, female, 70	The patient received Beriplex P/N 1750 IU for disseminated intravascular coagulation due to acute promyelocytic leukaemia. An additional dose of 1000 IU Beriplex P/N was given the next day. INR before first administration of Beriplex P/N was 1.7	The patient developed myocardial infarction ~4 h after first administration of Beriplex P/N
Case 15, female, 68	The patient received Beriplex P/N 1000 IU for haemostasis after aortic valve replacement and tricuspid/mitral valve replacement. One day later, patient received additional 500 IU of Beriplex P/N during re-opening of sternotomy for bleeding	One day after re-opening a CT scan showed bilateral small occipital infarcts. Subsequent medical records report bilateral retinal emboli
Case 16, female, 80	Patient received Beriplex P/N 1000 IU for postoperative bleeding after mitral valve repair and pulmonary vein isolation	Due to slow postoperative recovery, a CT was performed and showed a lacunar infarction in the right pons and left thalamus 12 days after surgery
Case 17, female, 79	The patient received 2× Beriplex P/N 1000 IU during cardiac surgery as the initial cardiopulmonary bypass time was prolonged	On the first postoperative day, cerebral ischaemia was diagnosed based on clinical symptoms (not confirmed by CT scan). The patient fully recovered within 24 h
Case 18, male, 77	The patient initially received 1000 IU followed by an additional 500 IU of Beriplex P/N during cardiac surgery as the initial cardiopulmonary bypass time was prolonged	On the first postoperative day, neurological deficit was diagnosed. A thromboembolic event was suspected based on clinical symptoms (not confirmed by CT scan). The patient fully recovered
Case 19, male, 88	The patient received Beriplex P/N 1000 IU due to ongoing microvascular bleeding after cardiac surgery	After operation, the patient made a slow neurological recovery. Four days postoperative, a CT scan showed a probable new cerebral infarction
Case 20, male, 70	The patient received Beriplex P/N 1000 IU on the first postoperative day after elective cardiac surgery. The INR was 1.93	One day after administration of Beriplex P/N, the patient developed myocardial infarction
Case 21, male, 77	The patient received Beriplex P/N 1000 IU before cardiac surgery (no anticoagulation therapy before hospital admission)	After operation, the patient made a slow neurological recovery. Eight days postoperative, a CT scan showed small peripheral infarcts in the cerebellar hemispheres bilaterally

circulatory arrest. All three patients suffering from thromboembolic events belonged to the control group without thromboelastometry-guided therapy and received intraoperative (IO) and postoperative (PO) transfusions—[means (range)] of packed red blood cells [IO: 8 units (4–11); PO: 5.2 (2–10)], fresh-frozen plasma (FFP) [IO: 8.2 units (5–10); PO: 9.2 units (2–20)], pooled platelet concentrates [IO: 2.2 units (2–3); PO: 1.6 (0–3)], fibrinogen concentrate [IO: 6.0 g (4–8); PO: 0.8 g (0–2)], and PCC [IO: 3600 IU (3000–4000); PO: 200 IU (0–1000)]—and also IO heparin and subsequent heparin reversal by protamine. No thromboembolic events were reported in the group with thromboelastometry-guided therapy. In all cases, the patients were severely ill and in a potentially pro-thrombotic state. This fact, and the high levels of blood product administration, means the reason for the reported thrombotic events was undetermined; however, PCCs cannot be ruled out as a potential cause.

In general, the PCCs reviewed were all found to be effective for the correction of the international normalized ratio (INR) in anticoagulated patients and the cessation of severe bleeding.[22 27 29 31–34 47 50 51] Within the emergency setting, the rapid correction of vitamin K antagonist therapy is required in patients with major bleeding or before invasive surgery. Evans and colleagues[27] carried out a prospective analysis of 10 anticoagulated patients requiring vitamin K antagonist reversal. PCC administration resulted in the immediate cessation of bleeding and a satisfactory clinical response in all patients. These data were

Table 3 Summary of clinical trials reporting four-factor PCC safety and efficacy. *CSL Behring, Marburg, Germany; †Octapharma, Vienna, Austria; ‡Sanquin, Amsterdam, The Netherlands; ¶Laboratoire Français du Fractionnment et des Biotechnologies, Courtaboeuf, France. AE, adverse event; AF, atrial fibrillation; INR, international normalized ratio; PCC, prothrombin complex concentrate

Study	Study type	Indication	Product	Patient number	Primary outcomes	Safety endpoints
Evans and colleagues[27]	Open label, prospective	Urgent vitamin K antagonist reversal	Beriplex P/N*	$n=10$	PCC infusion resulted in a reduction in the median INR from >20.0 (15.8–20.0) to 1.1 (1.0–1.3)	No thromboembolic or other AEs were reported
Preston and colleagues[33]	Open label, prospective	Urgent vitamin K antagonist reversal	Beriplex P/N*	$n=42$	PCC infusion resulted in a median reduction in INR from 3.98 (range 2.0–27.6) to ≤1.9 in all patients	No increase in D-dimer concentration was observed. No thromboembolic events occurred 7 days post-PCC infusion. One patient with severe peripheral vascular disease, sepsis, and renal and cardiac failure (Table 2) died of a thrombotic stroke after leg amputation 48 h after receiving Beriplex P/N. PCC could not be excluded as a contributory factor to thrombosis formation
Lorenz and colleagues[22]	Open label, prospective	Vitamin K-dependent clotting factor supplementation in severe liver disease	Beriplex P/N*	$n=21$	*In vivo* recovery of vitamin K-dependent clotting factors (II, VII, IX, and X) was 49.7–57.4%. Clinical efficacy was judged 'very good' in 76% of cases, and 'satisfactory' in 24%	No thrombotic events or evidence of pathogen transmission were observed
Lubetsky and colleagues[29]	Prospective, open label	Urgent vitamin K antagonist reversal	Octaplex†	$n=60$	Mean INR reduced from 6.1 (2.8) to 1.5 (0.3) 10 min post-PCC infusion. Clinical response to treatment rated as good in 85% of patients	Two seroconversion events for parvovirus B19 occurred. Pathogen transmission was judged as possibly related to PCC infusion. No thrombotic complications judged to be related to PCC infusion were observed
van Aart and colleagues[48]	Prospective, open label, randomized, controlled	Urgent vitamin K antagonist reversal	Cofact‡	$n=93$	The number of patients reaching the target INR 15 min after dosing was significantly higher than those receiving individualized PCC doses, compared with those treated with a standard dose (89% *vs* 43%; $P<0.001$)	Two cases of thrombotic stroke reported. One patient had a multi-infarct brain before PCC administration, and AF, hypertension, and vascular disease of the legs. The second patient had an AF and a large haematoma in the left leg before administration
Lorenz and colleagues[47]	Open label, prospective	Urgent vitamin K antagonist reversal	Beriplex P/N*	$n=8$	Mean INR reduced from 3.4 (±1.2) to <1.3 in seven patients (clinical efficacy rated 'very good') and <1.4 in one patient (clinical efficacy rated 'satisfactory')	No thrombotic events, anaphylactic, or allergic reactions, or other AEs were reported. No evidence of viral exposure was observed
Riess and colleagues[34]	Prospective, open label	Urgent vitamin K antagonist reversal	Octaplex†	$n=60$	Mean INR reduced to <1.4 in 91.5% of patients at 60 min post-infusion	One seroconversion event for parvovirus B19 occurred. Pathogen transmission was judged as possibly related to PCC infusion. No thrombotic complications judged to be related to PCC infusion were observed
Vigue and colleagues[35]	Prospective, observational	Immediate vitamin K antagonist reversal	Kaskadil¶	$n=18$	Mean INR reduced from 4.0 (1.6) at admission, to 1.2 (0.2) immediately after 20 IU kg^{-1} infused in 3 min	No clinical thrombotic events were observed, although systemic morphological investigations were not performed
Pabinger and colleagues[31 32]	Prospective, observational	Urgent vitamin K antagonist reversal	Beriplex P/N*	$n=43$	INR reduction to ≤1.3 was observed in 93% of patients at 30 min post-infusion. Infusion speed varied between 2.0 and 40.0 ml min^{-1}. No infusion effect on the INR achieved at 30 min was observed	A 70-yr-old male patient with metastatic gastrointestinal cancer and arrhythmia absoluta (Table 2) experienced fatal suspected pulmonary embolism judged to be possibly related to PCC administration (laboratory evidence indicated coagulation activation occurred before administration). Thrombogenicity marker pharmacokinetics were unaffected by infusion speed

corroborated by a larger prospective study (n=42), where the correction of INR to ≤1.9 was observed within 20 min of PCC administration.[33] The rapid infusion of PCCs [median dose 22.0 IU kg^{-1} (±3.0), total infusion time of 3 min] has been used for immediate anticoagulant reversal before neurosurgery in patients with ICH.[35] All patients displayed complete INR correction immediately after PCC bolus, allowing anticoagulated patients to be managed as rapidly as non-anticoagulated patients.[35] Pabinger and colleagues[32] investigated the impact of infusion speed upon the effectiveness of PCC administration for emergency reversal of vitamin K antagonist therapy. Infusion speeds of between 2.0 and 40.0 ml min^{-1} were used, and the resulting effects on INR and observed thrombogenicity marker pharmacokinetics were recorded. The infusion speed used had no effect upon the INR attained after 30 min, or on the plasma concentrations of thrombogenicity markers. This study provides the first prospective evidence that PCCs can be rapidly infused without impacting safety or efficacy.[32]

Clotting defects can result from severe liver damage, due to reduced levels of vitamin K-dependent coagulation factors.[52] Lorenz and colleagues[22] reported the administration of PCCs in 22 patients (median, 25.7 IU kg^{-1}) with impaired hepatic function, before urgent surgery or invasive procedure. The *in vivo* recovery of the substituted coagulation factors (FII, VII, FIX, FX, and protein C) was between 49.7% and 57.4%, with the clinician assessment of efficacy being either very good (76%) or satisfactory (24%). These findings, in conjunction with the lack of observed adverse reactions, led the study authors to conclude PCC administration in this cohort was both effective and well tolerated.

Discussion

During the period from February 1996 to March 2012, the reported number of serious AEs recorded in the Beriplex P/N pharmacovigilance database was low. A review of reported AEs from published clinical studies detailing Beriplex P/N administration shows that its use was associated with no anaphylaxis or allergic reactions, no virus transmission (6 months post-treatment), no cases of HIT type II, and a low incidence of clinically overt thromboembolic complications.[27 31–33 47] These figures are in line with the generally low incidence of AEs reported after the administration of other four-factor PCCs.

Thrombogenicity

PCCs are potent pro-coagulants, a property which has seen their increase in use in the emergency setting for anticoagulant reversal and the treatment of life-threatening bleeding. However, these products have historically carried a risk of thrombogenic events.[38 39] Three main risk factors that influence thrombotic potential in patients receiving PCCs for reversal of vitamin K-dependent anticoagulation have been identified.[39] First, predisposing factors including both pre-existing and current conditions can influence thrombosis. Since patients receiving PCCs to reverse anticoagulation therapy have an underlying tendency to thrombosis, such reversal is likely to increase the risk of thromboembolic events. Secondly, therapeutic factors such as concomitant surgery or the level of PCC dosing administered can increase risk. Finally, thrombogenesis may be influenced by the quality of the PCC preparation used, with the exclusion of activated coagulation factors and inclusion of anticoagulant agents (proteins C, S, Z, antithrombin, and heparin) of particular importance.[39]

Based on animal studies, the presence of heparin and antithrombin is suggested to be important for the effective neutralization of the activated forms of FIX and FX.[53] An *in vitro* analysis of the clotting factor constituents of PCCs found that FII (prothrombin) was the primary thrombogenic component present.[54] Moreover, the ratio of prothrombin administered relative to other coagulation factors was identified as a major determinant of thrombotic risk.[54] The coagulation factors present in PCCs differ in their half-lives, with prothrombin having by far the longest (50–80 h).[55] Consequently, a recent review of PCC thrombogenicity by Sørensen and colleagues[40] concluded that prothrombin accumulation associated with repeat doses of PCCs is the primary determinant of thrombotic risk. A biochemical comparison of several commercially available PCCs identified Beriplex P/N as well balanced for all four of coagulation factors present, containing the highest concentration of the therapeutic protein FX, while also being the most pure of all the products tested and possessing the greatest thrombin inhibition potential.[16] A clinical evaluation monitored the pharmacokinetics of PCC coagulation factors in healthy volunteers (n=15) post-Beriplex P/N administration. Large increases in clotting factors (II, VII, IX, and X) and anticoagulant proteins C and S were observed. Importantly, no increase in the thrombogenicity marker D-dimer was observed, nor was there any clinical evidence of thrombosis.

The current article represents an update to the data previously reviewed by Sørensen and colleagues, as more cases of thromboembolic events potentially associated with PCC administration are included. A total of 21 cases of thromboembolic events possibly related to PCC administration have been reported during the observation period reported here. In all of these 21 cases, patients were severely ill and a prothrombotic status is assumed. Even if a direct causal relationship between PCC administration and these thromboembolic events was supposed, the number is small with respect to the number of treatments (one in ~31 000). A recent meta-analysis of both three- and four-factor PCCs administered for the reversal of vitamin K antagonist therapy identified a low but quantifiable risk of thromboembolic complications associated with such therapy.[56] Overall, the rate of thromboembolic events across all studies was 1.4% [95% confidence interval (CI): 0.8–2.1], although this was slightly increased in patients receiving four-factor PCCs [1.8% (95% CI: 1.0–3.0)]. Reported thrombosis rates, even in those patients receiving anticoagulant therapies, can be as high as 24.4%, for example, after orthopaedic surgery.[57] It is therefore important to consider why the incidence of thromboembolic events reported in

this pharmacovigilance database is lower than others reported. The most likely explanation for the disparity relates to the under-reporting of such events in patients receiving PCC therapy. It is very important that physicians report any events they consider may be related to PCC administration to build the evidence base. One problem with such reporting is that it is often difficult to distinguish between thromboses resulting from PCC administration and those due to the pre-existing, unmasked prothrombotic condition for which patients were often receiving anticoagulant therapy originally.[58] It is important to balance the low risk of thromboembolism associated with PCC administration with its efficacy in treating life-threatening bleeding. A recent prospective study (n=160) analysed the efficacy and safety of PCCs [Beriplex P/N, Octaplex, or Prothromplex® (Baxter, Deerfield, IL, USA)] administered for the emergency reversal of vitamin K antagonist therapy due to bleeding or the need for urgent surgery. The clinical efficacy of PCC therapy was considered good in 91% of patients, while their administration was associated with a low risk of thromboembolic complications [3.8% (95% CI: 1.4–8.0%)].[58]

From a clinician's point of view, one might say that a way to reduce the risk of thromboembolic events could be a carefully reduced application of PCCs according to the clinical bleeding situation. Since regularly dosing is calculated by laboratory results, administration after clinical signs for bleeding might be favourable and full correction of INR seems not to be necessary in most cases. Furthermore, recently published data support the use of goal-directed therapy based on point-of-care thromboelastometric testing to reduce thromboembolic events.[21 49 59]

Pathogen transmission

Viral, bacterial, and prion protein transmission are important considerations in the transfusion of blood products, especially in the period after the widespread transmission of human immunodeficiency virus (HIV) and the emergence of variant Creutzfeldt–Jakob disease.[60] Dentali and colleagues[56] described an overall risk of viral transmission associated with PCC administration of 1.9% (95% CI: 0.3–4.9). It should be noted that the only incidences of viral transmission reported during this meta-analysis related to four cases of parvovirus B19 infection observed during two studies documenting Octaplex administration. Since receiving marketing authorization, no cases of pathogen transmission linked to Beriplex P/N administration have been reported. A two-step pathogen removal process during the manufacture of Beriplex P/N comprises both the pasteurization and nanofiltration of the concentrate, facilitating both viral inactivation and elimination, respectively.[61] These processes eliminate all viruses which have been tested for, most notably influenza virus (H5N2, H7N1, H1N1), bovine viral diarrhoea virus (specific model virus for hepatitis C virus), herpes simplex virus 1 (non-specific model virus for large enveloped DNA viruses), transmissible gastroenteritis virus (specific model virus for severe acute respiratory syndrome coronavirus), West Nile virus, canine parvovirus (model virus for parvovirus B19V), poliomyelitis virus type 1, HIV, and hepatitis virus (A and B variants). Monitoring of prion proteins during the purification process showed these to be significantly reduced.[61] In summary, pharmacovigilance data, in connection with published clinical studies and an assessment of purification processes, show Beriplex P/N to be well tolerated in relation to transfusion-transmitted pathogens.[22 27 31–33 47 61 62]

Efficacy

PCC infusion has also been shown to be more efficacious for the correction of INR compared with the established clinical practice of administering FFP.[28 30] Although not discussed in detail here, it is important to note that two of the major drawbacks related to FFP infusion are the high administration volumes required and the consequent slow rate of infusion.[32 63] Given the critical care settings in which PCCs are utilized, and the acute complications associated with anticoagulation therapy, the speed at which treatment can be administered is of paramount consideration. The treatment of trauma-related bleeding is one such setting where the administration of PCCs is increasing.[64 65] A retrospective analysis of trauma patients receiving PCC therapy in conjunction with fibrinogen concentrate revealed improved survival rates compared with those predicted by both the trauma injury severity score and the revised injury severity classification score.[65] In view of these initial results, there is a clear requirement for more prospective studies to further elucidate the efficacy of PCC administration as a therapeutic option in the treatment of trauma-related bleeding.

In conclusion, there exists broad agreement across published studies that four-factor PCCs are an efficacious and well-tolerated method of correcting coagulation factor deficiency in cases of vitamin K-dependent anticoagulation reversal and severe liver disease. A pharmacovigilance report detailing the 15 yr administration of Beriplex P/N across clinical settings shows this product to be both well tolerated and effective. After ~647 250 infusions, no cases of virus transmission or HIT type II possibly related to Beriplex P/N administration have been reported. Extensive data have demonstrated that the risk of thromboembolic events is low. These data are further supported by clinical data for the other commercially available four-factor PCCs. The low incidence of serious thromboembolic and other AEs is mitigated by their efficacy, in particular, the speed at which they are able to cessate bleeding in life-threatening situations.

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Declaration of interest

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