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Long-Term Safety of a Four-Factor Prothrombin Complex Concentrate (Kcentra®/Beriplex® P/N): An Updated Pharmacovigilance Review

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Abstract

Introduction Four-factor prothrombin complex concentrate (4F-PCC) is recommended for vitamin K antagonist reversal in patients with major bleeding or in need of surgery. The most important risk associated with the use of 4F-PCC is the occurrence of thromboembolic events (TEEs). In this review, we aim to evaluate the safety profile of a 4F-PCC (Kcentra®/Beriplex® P/N; CSL Behring, Marburg, Germany) by reviewing pharmacovigilance data.

Methods A retrospective analysis of postmarketing pharmacovigilance data of Kcentra®/Beriplex® P/N from February 1996 to April 2022 was performed and complemented by a review of clinical studies published between January 2012 and April 2022.

Results A total of 2,321,443 standard infusions of Kcentra®/Beriplex® P/N were administered during the evaluation period. Adverse drug reactions (ADRs) were reported in 614 cases (~1 per 3,781 standard infusions) and 233 of these cases (37.9%) experienced suspected TEEs related to 4F-PCC (~1 per 9,963 standard infusions); most of these cases had pre-existing or concomitant conditions likely to be significant risk factors for thrombosis. TEE rates were similar when 4F-PCC was used on-label or off-label for direct oral anticoagulant-associated bleeding. Thirty-six cases (5.9%) reported hypersensitivity type reactions (~1 per 64,485 standard infusions). No confirmed case of viral transmission related to 4F-PCC use was reported. The published literature also revealed a favorable safety profile of 4F-PCC.

Conclusion Analysis of postmarketing pharmacovigilance safety reports demonstrated that treatment with 4F-PCC was associated with few ADRs and a low rate of TEEs across multiple indications and settings, thus confirming a positive safety profile of 4F-PCC.

Keywords
- four-factor prothrombin complex concentrate
- safety
- pharmacovigilance
- oral anticoagulant reversal

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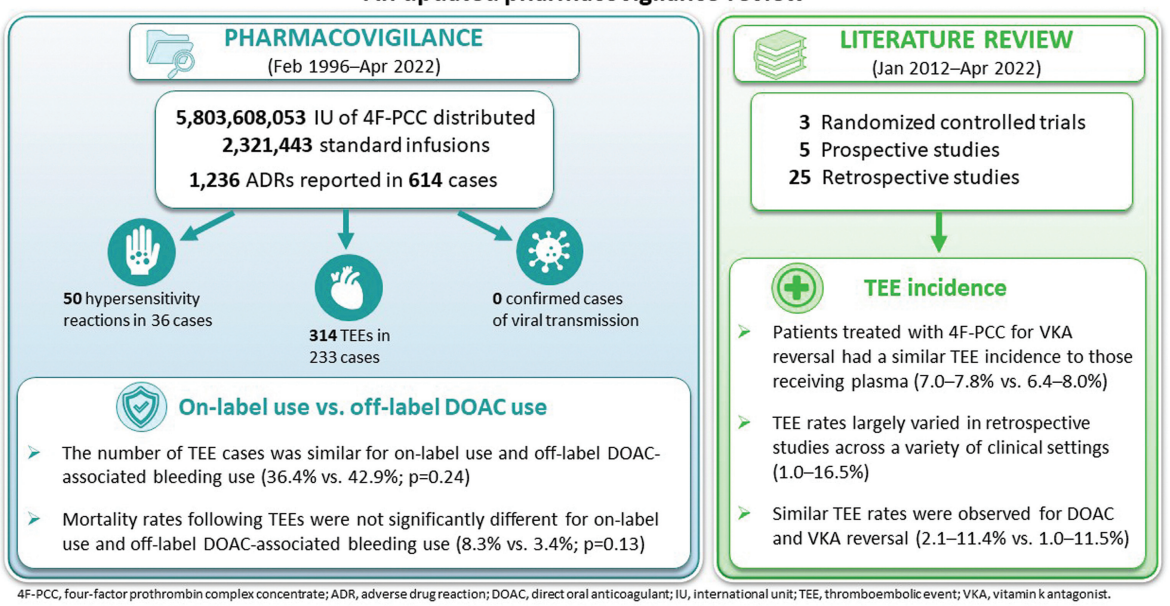

Visual summary.

Introduction

Guidelines recommend four-factor prothrombin complex concentrate (4F-PCC) for patients requiring rapid vitamin K antagonist (VKA) reversal due to major bleeding or urgent need for invasive surgery.[1–7] In addition, direct oral anticoagulants (DOACs) such as the activated factor X (FXa) inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban) and the direct thrombin inhibitor dabigatran have become more common in the management of patients at risk of thromboembolism.[8,9] Specific reversal agents for DOACs have recently become available, but recent guidelines also suggest off-label use of prothrombin complex concentrates (PCCs) for DOAC reversal when specific reversal agents are unavailable.[6,7,9–15] Patients receiving oral anticoagulants (OACs) such as VKAs and DOACs may be at increased risk for thrombosis due to their underlying condition when reversal agents are used. Consequently, there is clinical interest in the safety of 4F-PCC and other drugs used for reversal of OAC therapy, particularly with regards to the incidence of thromboembolic events (TEEs).

Beriplex® P/N is a 4F-PCC, manufactured by CSL Behring, which has been licensed across Europe since February 1996 for indications such as treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors and congenital deficiency of any of the vitamin K-dependent coagulation factors. The same product, marketed as Kcentra® in the United States, Japan, and elsewhere, was approved by the United States Food and Drug Administration in 2013 for the urgent reversal of VKA therapy in adult patients with acute major bleeding or a need for urgent surgery or invasive procedures.[16] The safety of Kcentra®/Beriplex® P/N had been previously examined with a retrospective review of pharmacovigilance data and of the literature between February 1996 and March 2012.[17] However, when the 2013 pharmacovigilance study was published, Kcentra® had not been launched in the United States and 4F-PCCs were—at that time—not as commonly used in clinical practice for DOAC reversal as nowadays. Therefore, the current manuscript provides a review of the pharmacovigilance data from February 1996 to April 2022. To complement the pharmacovigilance findings, a literature search was performed to identify additional studies reporting safety data for Kcentra®/Beriplex® P/N in OAC reversal, as well as other relevant clinical settings, such as severe liver disease, transplant, massive transfusion protocol, and bleeding and surgery of nonanticoagulated patients.

Methods

Analysis of Pharmacovigilance Data

A retrospective review of the global pharmacovigilance database of CSL Behring between 16 February 1996 and 30 April 2022 was performed. The review included spontaneous reports, reports from postmarketing studies, reports from regulatory agencies, and cases identified from the review of the literature. Only adverse events (AEs) where a suspected causal relationship could not be excluded between Kcentra®/Beriplex® P/N and occurrence (adverse drug reactions [ADRs]) were included.

All reported ADRs for Kcentra®/Beriplex® P/N were analyzed and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25. For each ADR case report, the year, country of origin, patient age and sex, indication, Kcentra®/Beriplex® P/N dose, concomitant products,

manifestations, and outcome of the ADR were recorded if available. Each case report may contain multiple AEs. The cumulative quantity of 4F-PCC distributed during the study period was established from CSL Behring commercial records. Patient exposure is presented as number of estimated 2,500 IU single standard doses based on the units distributed. Additional methodology used in retrieving pharmacovigilance data is summarized in the ►**Supplementary Materials**.

Statistical Analysis

All analyses compared Kcentra®/Beriplex® P/N on-label use and off-label use in which DOAC-associated bleeding was reported. Some outcomes were measured at the case level (i.e., one observation per case) and others were measured at the ADR level (i.e., one observation per ADR). All outcomes where there were sufficient data to perform a statistical comparison were measured on a categorical scale. The Chi-square test was used to compare between on-label and off-label DOAC reversal groups for the majority of outcomes. The exception was for outcomes that were rarely observed, where Fisher's exact test was preferred.

Review of 4F-PCC Safety

A literature review was performed using the PubMed database to assess the safety of Kcentra®/Beriplex® P/N. The search string used was ("prothrombin complex concentrate" OR "prothrombin complex concentrates" OR "4F-PCC") AND ("safety" OR "reversal" OR "thrombosis" OR "embolism"). The PubMed search was restricted to the period January 2012 to April 2022 to update the findings of the previously published review by Hanke et al.[17] Prospective studies published before 2012 and previously reviewed in the 2013 study were also included and summarized in context of the updated findings. Clinical studies identified in the search and reporting AEs were reviewed. Relevant information relating to clinical indication, dosage, reversal for VKA or DOAC (or other indication), and AEs relating to Kcentra®/Beriplex® P/N were identified. Additional details on the literature search are described in the ►**Supplementary Materials**.

Results

Pharmacovigilance

Baseline Characteristics

A total of 5,803,608,053 IU of Kcentra®/Beriplex® P/N were administered during the period of evaluation, corresponding to 2,321,443 standard infusions of 2,500 IU, across a range of clinical settings and indications worldwide. Kcentra®/Beriplex® P/N were registered in 49 countries across Europe, Asia, America including the United States, Canada, and South America. A summary of the pharmacovigilance data extracted for Kcentra®/Beriplex® P/N is detailed in ►**Supplementary Table S1** (available in the online version).

Nature and Rate of Adverse Drug Reactions

Between 21 February 1996 and 30 April 2022, a total of 1,236 ADRs in 614 cases were reported from postmarketing sources for Kcentra®/Beriplex® P/N. The 614 cases reported for Kcentra®/Beriplex® P/N corresponded to approximately one case per 9,452,130 IU distributed or for every 3,781 standard infusions administered. Of the 1,236 ADRs reported for Kcentra®/Beriplex® P/N, 1,003 events (81.1%) were classified as serious ADRs according to regulatory definition. These cases included events considered to be important identified risks, such as anaphylaxis and hypersensitivity/allergic reactions and TEEs, or potential risks, such as suspicion of virus transmission.

When assessing Kcentra®/Beriplex® P/N use for on-label indications versus off-label (DOAC-associated bleeding), the cumulative number of cases reported for on-label use was 495 (81% of all cases) and for off-label use 119 (19% of all cases), with 91 of the off-label cases related to DOAC-associated bleeding (►**Table 1**).

Out of the 614 cases, a total of 131 fatal cases were reported with 122 cases (93.1%) assessed as related to Kcentra®/Beriplex® P/N. The most common primary indications for the related fatal cases were all types of hemorrhage ($n = 26$), anticoagulant therapy ($n = 7$), surgery ($n = 7$), and procoagulant therapy ($n = 6$). Fifty out of 122 cases (41.0%) concerned elderly patients (≥65 years) with underlying conditions and concomitant medications that may have contributed to the fatal outcomes. Among fatal ADRs, the most commonly reported causes of death were TEEs ($n = 71$), drug ineffectivity ($n = 23$), and all types of hemorrhage ($n = 21$). The number of fatal cases related to Kcentra®/Beriplex® P/N on-label use was 97 (19.6% of all on-label cases) compared with 17 fatal cases (18.7% of all off-label DOAC cases) for off-label Kcentra®/Beriplex® P/N use for the management of DOAC-associated bleeding (►**Table 1**). The remaining eight fatal cases pertained to off-label use of Kcentra®/Beriplex® P/N that was not related to administration of DOACs.

Anaphylaxis and Hypersensitivity/Allergic Reactions

Fifty related anaphylaxis and hypersensitivity/allergic reactions were identified from 36 cases (5.9% of all cases); this is approximately one case reported per 161,211,335 IU of Kcentra®/Beriplex® P/N distributed or for every 64,485 standard infusions. Hypersensitivity reactions were reported in 22 male patients and 12 female patients (gender unspecified in 2 cases). The age was reported for 29 patients, with a median (interquartile range [IQR]) age of 67 (54–76) years. The most commonly reported hypersensitivity ADRs were hypersensitivity ($n = 9$), rash ($n = 7$), anaphylactic reaction ($n = 6$), urticaria ($n = 6$), shock ($n = 5$), and circulatory collapse ($n = 4$). Forty-eight hypersensitivity/allergic reactions in 34 cases were reported in association with on-label use of Kcentra®/Beriplex® P/N, whereas no cases were reported for off-label use for the management of DOAC-associated bleeding (►**Table 1**).

Thromboembolic Complications

A total of 233 cases (37.9% of all cases) describing 314 suspected TEEs related to Kcentra®/Beriplex® P/N were reported; of these, 131 (56.2%) were case reports from the scientific literature, 53 (22.8%) were study reports, 38 (16.3%) were spontaneous reports, and 11 (4.7%) were

Table 1 Case level analysis: comparison of ADRs for on-label use of Kcentra®/Beriplex® P/N versus off-label use for the management of DOAC-associated bleeding

	On-label use ($n = 495$), *n* (%)	Off-label DOAC-associated bleeding ($n = 89$)[a] *n* (%)	*p*-Value
Fatal ADR case	97 (19.6)	17 (18.7)	0.84
Hypersensitivity reactions	34 (6.9)	0 (0.0)	**0.01**
TEEs	180 (36.4)	39 (42.9)	0.24
Fatal TEE cases	41 (8.3)	3 (3.4)	0.13
Age, years[b]	74.0 (6.0–94.0)	79.5 (43.0–84.0)	–
Patient age group[c]			0.20
Elderly (≥65 years)	97 (71.3)	13 (92.9)	
Adults (18–64 years)	38 (27.9)	1 (7.1)	
Children (0–17 years)	1 (0.7)	0 (0.0)	

Abbreviations: ADR, adverse drug reaction; DOAC, direct oral anticoagulant; TEE, thromboembolic event.
Note: Statistically significant *p*-value is indicated in bold.
[a]Data missing for two cases.
[b]Median (data range) reported.
[c]Data only available for 136 on-label cases, 14 off-label DOAC cases.

reports from regulatory authorities (►**Table 2**). Forty-seven out of 53 study cases (88.7%) were from a drug use results survey for Kcentra® in Japan. Within the context of total infusions administered, this corresponds to a ratio of 1 case involving one or more TEEs per approximately 9,963 standard infusions. The age was reported for 161 patients; median (IQR) age was 74 (62–82) years. The sex was reported for 168 patients and female/male ratio was 0.58. The most commonly reported primary indications included hemorrhage ($n = 75$; all types including prophylaxis, postprocedural, intracranial, cerebral, gastrointestinal), procoagulant therapy ($n = 58$), anticoagulant therapy ($n = 21$), product used for unknown indication ($n = 16$), and surgery ($n = 15$). An analysis of these cases revealed that 94 (40.3% of all TEE cases) concerned elderly patients with pre-existing or concomitant conditions likely to be significant risk factors for thrombosis. A total of 113 out of the 233 TEE cases reported information on the patient's medical history, 49 cases included atrial fibrillation. Of the 233 cases reported, 48 (20.6% of all TEE cases) had a fatal outcome related to a TEE. Some thrombosis-associated deaths resulted in multiple thromboembolism: across the fatal TEEs, there were 16 instances of arterial TEEs (22.5%), 16 of venous TEEs (22.5%), while 39 (55.0%) were unspecified or mixed arterial/venous TEEs.

Table 2 Details of suspected thromboembolic events related to Kcentra®/Beriplex® P/N administration from the pharmacovigilance database

Details of TEEs reported as related to Kcentra®/Beriplex® P/N administration	
Number of TEE cases	233
Mean (IQR) age of patients, years[a]	74 (62–82)
Female/male patient ratio[b]	0.58
TEEs with medical history of atrial fibrillation, *n* (%)	49 (21)
Reason for Kcentra®/Beriplex® P/N use, *n* (%)	
Hemorrhage[c]	75 (32.2)
Procoagulant therapy	58 (24.9)
Anticoagulant therapy	21 (9.0)
Surgery	15 (6.4)
Unknown indication	16 (6.9)
Fatal TEEs,[d] *n* (%)	48 (20.6)

Abbreviations: IQR, interquartile range; TEE, thromboembolic event.
[a]Age and sex were reported for 161 and 168 patients (female 62, male 106), respectively.
[b]Reported for 185 patients.
[c]All types, including prophylaxis, postprocedural, intracranial, cerebral, gastrointestinal, etc.
[d]Additional risk factors existed in all cases, which provide alternative explanations.

A further breakdown of the 233 TEE cases indicated that 257 events in 180 cases concerned on-label use (36.4% of all on-label cases) and 42 events in 39 cases were related to off-label DOAC-associated bleeding use (42.9% of all off-label DOAC cases) (►**Tables 1** and **3**). The number of events was higher than the number of cases in both groups indicating that some patients experienced more than one TEE. This occurred in 45 out of the 180 (25.0%) on-label cases and in 3 out of the 39 (7.7%) off-label DOAC cases. The remaining 14 cases related to off-label use of 4F-PCC which was not associated with DOACs. In both groups, a large percentage of cases concerned elderly patients (71.3% on-label; 92.9% off-label DOAC). A total of 41 TEE cases were fatal for on-label use compared with 5 fatal cases for off-label DOAC-associated bleeding use (►**Table 1**). There was no significant group difference at the case level analysis for the occurrence of TEEs or fatal TEEs (►**Table 1**). However, the results suggest a statistically significant difference in the occurrence of TEEs between the two cohorts at the ADR level analysis (►**Table 3**). TEEs were more common in the

Table 3 ADR level analysis: comparison of ADRs for on-label use of Kcentra®/Beriplex® P/N versus off-label use for the management of DOAC-associated bleeding

	On-label use ($n = 1,067$), n (%)	Off-label DOAC-associated bleeding ($n = 112$), n (%)	p-Value
Hypersensitivity reactions	48 (4.5)	0 (0.0)	**0.02**
TEEs	257 (24.1)	42 (37.5)	**0.002**
Most reported TEEs			
Stroke[a]	63 (5.9)	9 (8.0)	0.37
DVT	31 (2.9)	11 (9.8)	**<0.001**
MI[b]	21 (2.0)	5 (4.5)	0.09
Pulmonary embolism	18 (1.7)	4 (3.6)	0.15
DIC	10 (0.9)	1 (0.9)	1.00
TEE outcome[c]			0.20
Recovered/resolved	50 (29.8)	1 (7.7)	
Recovering/resolving	19 (11.3)	1 (7.7)	
Recovered/resolved with sequelae	18 (10.7)	4 (30.8)	
Recovered with treatment	1 (0.6)	0 (0.0)	
Not recovered/not resolved	17 (10.1)	1 (7.7)	
Fatal	63 (37.5)	6 (46.2)	
Not reported/unknown	89	29	

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; ADR, adverse drug reaction; DIC, disseminated intravascular coagulopathy; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; MI, myocardial infarction; TEE, thromboembolic event.
Note: Statistically significant p-values are indicated in bold.
[a]Including ischemic stroke, embolic stroke, thrombotic stroke, cerebral infarction, embolic cerebral infarction, ischemic cerebral infarction, and cerebrovascular accident.
[b]Including acute myocardial infarction.
[c]Analysis based on occurrences of TEE only ($n = 257$ on-label; $n = 42$ off-label DOAC).

off-label DOAC-associated bleeding group, whereby 37.5% of ADRs resulted in a TEE compared with 24.1% in the on-label group ($p = 0.002$; ►**Table 3**).

The most reported TEE complications for both 4F-PCC on-label use and off-label DOAC-associated bleeding use were stroke and deep vein thrombosis (DVT) (►**Table 2**). The two groups did not vary significantly in the occurrence of stroke, myocardial infarction, pulmonary embolism, or disseminated intravascular coagulopathy. However, DVT was significantly more common in the off-label DOAC-associated bleeding group, occurring in 9.8% of ADRs, compared with 2.9% of ADRs in the on-label group (►**Table 3**). Atrial fibrillation was included in the medical history of 24.5 and 26.2% of on-label and off-label DOAC TEEs, respectively. A complete breakdown of all TEEs extracted from the pharmacovigilance database for on-label ($n = 257$) and off-label DOAC ($n = 42$) TEEs is reported in ►**Supplementary Tables S2** and **S3** (available in the online version). Most TEE outcomes were unknown for both on-label use (34.6%) and off-label DOAC-associated bleeding use (69.0%) while among those reported, the majority had a fatal outcome (►**Table 3**). For ADRs where a TEE occurred, the outcome of the TEE did not significantly vary between the two cohorts. A small fraction of cases (39.1% of all TEE cases; 41.1 and 23.1% of all on-label and off-label DOAC cases, respectively) reported information regarding time of TEE onset; details are included in ►**Supplementary Table S4** (available in the online version).

Suspicion of Virus Transmission

A total of 28 cases (4.6% of all cases) of suspected viral transmissions were reported; however, no case was confirmed as related to Kcentra®/Beriplex® P/N administration.

Literature Review

Safety Outcomes from Randomized Controlled Trials and Prospective Studies

A summary of randomized controlled trials (RCTs) and studies reporting prospective data on the safety of Kcentra®/Beriplex® P/N, including the prospective studies previously summarized in the 2013 pharmacovigilance study, is shown in ►**Table 4**. These included two studies on VKA reversal in patients with major bleeding,[18,19] one study on VKA reversal in patients requiring an urgent surgical/invasive procedure,[20] five studies on VKA reversal in patients with major bleeding or in need of urgent surgery,[21–25] one study on VKA reversal,[26] and one study on vitamin K-dependent coagulation factor supplementation in severe liver disease.[27] An additional single-arm phase 3b study conducted in Japanese patients[28,29] was identified but excluded from the final review as only a very small number of patients with major bleeding ($n = 6$) or in need of urgent surgical/invasive procedures ($n = 5$) were assessed.[28,29]

A post-hoc analysis of data from the two prospective phase 3b trials[18,20] compared the TEE incidence after VKA

Table 4 Summary of randomized controlled trials and studies reporting prospectively collected data on the safety of Kcentra®/Beriplex® P/N

Study	Study type	Indication	Dose	Summary of AEs		
Randomized controlled studies						
Sarode et al[18,a]	RCT of Beriplex® P/N vs. plasma	VKA reversal in patients with major bleeding	Beriplex® P/N (infusion rate ≤3 IU/kg per minute) based on body weight and INR	Events, *n* (%)	Treatment group	
					Beriplex® P/N (*n* = 103)	Plasma (*n* = 109)
				Any non-serious AE	66 (64.1)	71 (65.1)
				Any SAE	32 (31.1)	26 (23.9)
				Deaths to Day 45	10 (9.7)	5 (4.6)
				TEEs	8 (7.8)	7 (6.4)
				Fluid overload or similar cardiac event	5 (4.9)	14 (12.8)
Goldstein et al[20,a]	RCT of Kcentra®/Beriplex® P/N vs. plasma	VKA reversal in patients requiring urgent surgical/invasive procedures	Kcentra®/Beriplex® P/N (infusion rate ≤3 IU/kg per minute) based on body weight and INR	Events, *n* (%)	Treatment group	
					Kcentra®/Beriplex® P/N (*n* = 88)	Plasma (*n* = 88)
				Any AE	49 (56)	53 (60)
				AE related to treatment	8 (9)	15 (17)
				AE that led to treatment discontinuation	0	0
				Any SAE	22 (25)	23 (26)
				Deaths until Day 45	3 (3)	8 (9)
				TEEs	6 (7)	7 (8)
				Fluid overload or similar cardiac event	3 (3)	11 (13)
				Bleeding after primary outcome evaluation	3 (3)	4 (5)
Stoecker et al[23]	RCT of fixed dose vs. variable dose Kcentra®	Warfarin reversal in patients with emergent bleeding or needing urgent surgery	Fixed dose of 1,500 IU (*n* = 34) vs. standard variable dose based on body weight and INR (*n* = 37)	There were no TEEs in any patient for the first 7 days after Kcentra® administration, so no differences in safety could be reported		

Table 4 (*Continued*)

Study	Study type	Indication	Dose	Summary of AEs
Prospective studies				
Pabinger et al[21,22]	Prospective, observational ($n=43$)	Urgent VKA reversal in patients with major bleeding or before urgent surgical/invasive procedures	Beriplex® P/N dose based on INR	1/43 (2.3%) patient experienced a fatal suspected pulmonary embolism
Evans et al[19]	Open label, prospective ($n=10$)	Urgent VKA reversal in patients with major bleeding	Beriplex® P/N 30 IU over 10–15 minutes	There were no reported TEEs or other AEs
Preston et al[26]	Open label, prospective ($n=42$)	Urgent VKA reversal	Beriplex® P/N dose based on INR	No TEEs occurred until 7 days postinfusion
Lorenz et al[27]	Open label, prospective ($n=21$)	Vitamin K-dependent clotting factor supplementation in severe liver disease	One or two Beriplex® P/N infusions (median dose 1,500 IU for the first infusion [$n=21$]; 2,000 IU for the second infusion [$n=5$]; median infusion rate was 150 IU/min)	No TEEs or evidence of pathogen transmissions were observed
Lorenz et al[24]	Open label, prospective ($n=8$)	Urgent VKA reversal in patients with major bleeding or needing urgent surgery	Beriplex® P/N dose based on defect severity, bleeding extent and location, and clinical presentation	There were no TEEs, consumption coagulopathy, anaphylactic or allergic reactions, or other AEs
Bitonti et al[25]	Retrospective cohort receiving a variable dose of Kcentra® ($n=30$) Prospective cohort receiving a fixed dose of Kcentra® ($n=24$)	Urgent VKA reversal in patients with major bleeding or needing urgent surgery	Standard variable dose based on body weight and INR Fixed dose of 1,500 IU	No TEEs reported in either cohort within 7 days of Kcentra® administration
Schenk et al[70]	Open label, prospective ($n=13$)	Patients with life-threatening bleedings receiving rivaroxaban	Beriplex® P/N 25 IU/kg of body weight as bolus or continuous infusion	No TEEs reported within 7 days of Beriplex® P/N administration Three deaths were reported, all unrelated to Beriplex® P/N. One from septic shock, one due to progressive cancer, and one from intracranial hemorrhage

Abbreviations: AE, adverse event; INR, international normalized ratio; IU, international unit; PCC, prothrombin complex concentrate; RCT, randomized controlled trial; SAE, serious adverse event; TEE, thromboembolic event; VKA, vitamin K antagonist.

[a]The study was not powered to demonstrate significant differences between groups for safety outcomes.

reversal with Kcentra®/Beriplex® P/N or plasma in patients with major bleeding or in need of urgent surgery.[30] The TEE incidence was similar and independent of coagulation factor levels, indicating no increased TEE risk.[30] Overall, 7.3% in the pooled Kcentra®/Beriplex® P/N group and 7.1% in the pooled plasma group experienced ≥1 TEE (difference: 0.2%; 95% confidence interval [CI]: −5.5 to 6.0%).[30] The risk of TEE was not proportional to Kcentra®/Beriplex® P/N dose and the study product dose was not associated with TEE development in either treatment group.[30] A separate pooled safety analysis of data from the two phase 3b studies compared the overall safety profile of Kcentra®/Beriplex® P/N versus plasma.[31] More patients in the plasma group had fluid overload, cardiac failure, and pulmonary edema than in the Kcentra®/Beriplex® P/N group (12.7 vs. 4.7%).[31] This is congruent with another post-hoc analysis showing that, after adjusting for other potential risk factors, plasma use was independently associated with a greater risk of volume overload than Kcentra®/Beriplex® P/N (odds ratio: 2.74; 95% CI: 1.21–6.19; $p = 0.02$).[32] No viral transmission was confirmed for Kcentra®/Beriplex® P/N.[31] There were 13 (6.8%) and 13 (6.6%) deaths in the Kcentra®/Beriplex® P/N group and in the plasma group, respectively.[31] Another post-hoc analysis evaluating the impact of Kcentra®/Beriplex® P/N versus plasma on time to procedure in patients with gastrointestinal bleeding reported a shorter median time to procedure with Kcentra®/Beriplex® P/N compared with plasma (17.5 vs. 23.9 hours, respectively; $p = 0.037$); safety outcomes were consistent with the results from the two phase 3b trials.[18,20,33]

Prospective studies reported lower incidence of TEEs than the phase 3b studies (0–2.3% vs. 7–7.8%, respectively; see ►**Table 4** for further details).[19,21,22,24,26,27]

Safety Outcomes from Retrospective Studies

The outcomes of 25 retrospective studies identified in the literature search are summarized in ►**Supplementary Table S5** (available in the online version). Among retrospective studies, the majority ($n = 11$) reported safety outcomes of 4F-PCC in patients requiring VKA reversal,[34–44] including three studies comparing fixed and standard variable dosing,[34–36] one study investigating VKA reversal for intracranial hemorrhage (ICH),[39] and one study comparing outcomes in patients with body weight over or under 100 kg.[40] Nine studies reporting the use of 4F-PCC for OAC (VKA or DOAC) reversal were retrieved,[45–53] including three studies examining 4F-PCC for reversal of VKA or DOAC-associated ICH[48,52,53] and one study comparing use of 4F-PCC for on-label and off-label indications.[51] Two studies specifically investigated 4F-PCC as DOAC reversal therapy,[54,55] while three studies reported safety outcomes of 4F-PCC in non-anticoagulated patients.[56–58]

The incidence of TEEs reported in the VKA reversal retrospective studies ranged from 1.0 to 11.5%, which was similar to that seen in the phase 3b clinical trials.[34–44] Similarly, TEE rates ranged from 2.1 to 11.4% when Kcentra®/Beriplex® P/N was used for the management of DOAC-associated bleeding.[48,49,53–55] When used for VKA reversal, there were no consistent findings of fixed or standard variable dosing having an effect on the incidence of TEEs,[34,36,39,43,44] including comparisons of patients with body weight over or under 100 kg.[40] In nonanticoagulated patients treated with Kcentra®/Beriplex® P/N, the incidence of TEEs ranged from 1.3 to 3.4%.[56–58]

Mortality rates across the retrospective studies ranged from 7.6 to 30.4% in VKA studies and 13 to 40.9% in DOAC-associated bleeding studies. No difference in mortality rates was detected in studies directly comparing VKA reversal versus DOAC reversal,[48,49,51] with only one study reporting higher mortality rates for off-label versus on-label indications (37.7 vs. 19.1%, respectively; $p = 0.01$).[46] In studies with nonanticoagulated patients, mortality rates ranged from 3.3 to 26.0% (►**Supplementary Table S4**, available in the online version).[56–58]

Discussion

Overall, analysis of over 26 years of Kcentra®/Beriplex® P/N pharmacovigilance data indicated a low rate of ADRs, with only 614 cases reported, equivalent to 1 case per 9,452,130 IU distributed or 1 every 3,781 infusions. This is consistent with the previous review of the safety of Beriplex® P/N where a low rate of AEs was reported.[17]

A total of 122 fatal cases assessed as related to Kcentra®/Beriplex® P/N were reported. Fifty of these concerned elderly patients (≥65 years) with underlying conditions and concomitant medications that may have been contributory to the fatal outcomes. However, 51 of the cases did not report specific case information to determine what contributed to the fatalities. TEEs were the most common cause of death representing 28.4% of all fatal ADRs. Pooled safety data from two phase 3b trials showed no difference in fatality rates between Kcentra®/Beriplex® P/N and plasma-treated patients requiring rapid VKA reversal because of acute major bleeding or before emergency surgery.[18,20,31] Multiple retrospective studies reported fatalities, although only a small number were considered related to Kcentra®/Beriplex® P/N.[37,42,52,56]

Patients treated with OAC therapy have conditions that predispose them to experience thromboembolic complications. As such, rapid anticoagulation reversal therapy may increase their risk of developing TEEs, especially when restart of anticoagulation is delayed or even completely withdrawn.[31] This is crucial in patients experiencing ICH since, on average, anticoagulation is resumed 4 to 6 weeks after the acute event.[59] Among the total reported cases, 233/614 (37.9%) experienced TEEs, of which 48/233 (20.6%) were fatal. However, most of these cases concerned patients with underlying conditions or concomitant risk factors. In line with the pharmacovigilance findings, data from the two RCTs indicated that patients experiencing TEEs had a variety of underlying risk factors, with the most frequent being hypertension, atrial fibrillation, coronary artery disease, and congestive heart failure.[30]

There was a large variation of TEE rates across the retrospective studies, showing TEE incidences in the range of 1.0 to 16.5% in a variety of clinical settings, including OAC reversal, nonanticoagulated patients, and as part of massive transfusion protocols.[34–51,53–56,58]

A recent multicenter observational study reported on the short-term risks of TEE in a large, matched, real-world cohort of adults receiving 4F-PCC or plasma for VKA-associated major bleeding.[60] The risk of confirmed arterial or venous TEE after 4F-PCC therapy (3.5%; 95% CI: 2.5–4.7%) was similar to that of plasma (4.5%; 95% CI: 3.3–5.9%).[60] The adjusted risk of all-cause mortality at 45 days posttreatment was lower in patients receiving 4F-PCC compared with a matched historical cohort receiving plasma.[60] Studies that have investigated fixed doses versus variable doses of Kcentra®/Beriplex® P/N for VKA reversal showed little difference in TEEs.[23,25,35,36,39,40,43,44] One study showed a slight increase in TEEs with fixed dose (16%) compared with variable dose (6%).[34] This is an important finding as fixed dosing of 4F-PCC instead of weight-dependent dosing can be more cost effective, while still as effective at controlling bleeding and restoring hemostasis.[61–65]

Clinical practice guidelines suggest off-label use of PCCs for management of DOAC-associated bleeding, specifically of oral FXa inhibitors, when specific reversal agents are not available.[6,7,10–13] This is supported by the published literature which shows that 4F-PCC and andexanet alfa, the specific reversal agent of FXa inhibitors, may have comparable hemostatic efficacy, albeit andexanet alfa appears to be associated with higher TEE rates.[66–68] Retrospective studies have shown a relatively low incidence of TEEs when 4F-PCC was used off-label for DOAC reversal;[48,49,53–55] these rates are comparable with those observed in 4F-PCC use for VKA reversal.[34–44,48,49] In addition, a few studies reported a similar TEE incidence when 4F-PCC was used for VKA or DOAC reversal.[48,49,51] In particular, one study found no differences in TEE rates when 4F-PCC was used for the management of either warfarin- or DOAC-associated ICH (9.6% for warfarin vs. 11.4% for DOAC).[48] Consistent with the published literature, the review of pharmacovigilance data has shown that TEE complications represented a similar proportion of 4F-PCC patients for on-label use and off-label DOAC-associated bleeding use. However, significantly more ADRs resulted in a TEE in the off-label DOAC-associated bleeding group compared with the on-label group. Interestingly, stroke and DVT complications accounted for the majority of TEEs in both on-label use and off-label DOAC-associated bleeding use. This is in line with the results of a large multicenter observational study of adults receiving 4F-PCC for VKA reversal, in which the most reported TEEs were DVT and stroke.[60] Similarly, in the study by Makhoul et al,[45] DVT and stroke were the most reported TEEs in patients receiving 4F-PCC for either DOAC or warfarin reversal representing 62 and 28% of TEEs, respectively.[45] Here, pharmacovigilance data suggested that DVT was significantly more common in the off-label DOAC-associated bleeding group compared with the on-label group.

Pharmacovigilance reports also indicated that there were no significant differences in mortality rates following TEE complications in the 4F-PCC on-label use and off-label DOAC-associated bleeding groups. This is in general agreement with several retrospective studies, in which mortality rates were not affected by 4F-PCC indication.[48,49,51] In contrast, higher mortality rates for 4F-PCC off-label versus on-label indications have been reported in two studies.[46,69] These included the study by Naeem et al,[46] which was identified in our search, and a more recently published large cohort study in which markedly higher in-hospital mortality rates were observed in patients receiving 4F-PCC for off-label indications compared with those receiving it for on-label use (29 vs. 18%).[69]

Limitations

It is important to highlight that pharmacovigilance data may be affected by the potential underreporting of ADRs as the process is voluntary and provision of details required for assessment is not mandatory. Therefore, often cases do not include all details, such as patient demographics, primary indications, concomitant medications, or presence of thrombotic risk factors. Another limitation of pharmacovigilance surveillance is that ADR reports do not confirm a cause-and-effect relationship with treatment. In addition, it should be noted that the pharmacovigilance ADR rates were estimated assuming 2,500 IU as the average dose per 4F-PCC infusion. Although this may be valid for the majority of the cases which were on-label, doses used for the management of DOAC-associated bleeding may be higher and ranging between 2,500 and 5,000 IU.[49] Finally, large differences in population sizes across the various published studies may hinder comparison between reversal strategies.

Conclusion

This updated review of postmarketing pharmacovigilance safety reports has shown that treatment with 4F-PCC was associated with few ADRs and a relatively low rate of TEEs across multiple indications and settings including off-label use for the management of DOAC-associated bleeding, thus confirming a favorable safety profile of 4F-PCC.

What is known about this topic?

- Four-factor prothrombin complex concentrate (4F-PCC) is recommended for urgent vitamin K antagonist (VKA) reversal in patients with major bleeding or in need of surgery.
- Patients receiving anticoagulants may be at increased risk for thrombosis due to their underlying condition when reversal agents are used.
- Therefore, there is clinical interest in the safety of 4F-PCCs particularly regarding thromboembolic events (TEEs).

What does this paper add?

- Analysis of pharmacovigilance reports of a 4F-PCC (Kcentra®/Beriplex® P/N) collected over 26 years of surveillance indicates that use of 4F-PCC was associated with a low incidence of TEEs.
- In addition, a review of the literature confirms the favorable safety profile of 4F-PCC.
- This study reaffirms the long-term safety of 4F-PCC when used across various settings, including VKA and direct oral anticoagulant reversal.

Conflict of Interest
T.J.M. is a consultant for CSL Behring, Octapharma, Alexion-Astra Zeneca, and Cellphire. E.L.-L. has received lecture honoraria and advisory fees from Astra Zeneca, Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Portola, Norgine, Roche, CSL Behring, Viatris, and Aspen and institutional research support from Bayer AG, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, and CSL Behring. A.V. and D.S.S. are employees of CSL Behring.

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