

Safety of a pasteurized plasma-derived Factor VIII and von Willebrand factor concentrate: analysis of 33 years of pharmacovigilance data

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BACKGROUND: Haemate-P/Humate-P (Humate-P) is a pasteurized human plasma-derived concentrate containing both Factor VIII and von Willebrand factor for treatment of hemophilia A and von Willebrand disease (VWD).

STUDY DESIGN AND METHODS: We analyzed the safety of Humate-P based on more than 33 years of postmarketing pharmacovigilance data, representing an estimated exposure of approximately 25,000 patient-years. The analysis comprises reports of potential adverse drug reactions (ADRs) from all sources, reported as part of routine pharmacovigilance at CSL Behring. ADRs considered clinically relevant or potential risks of Humate-P were identified based on defined and standardized Medical Dictionary for Regulatory Activities queries. Recognizing the limitations of spontaneous reporting, we also reviewed the literature, including clinical trials with mandatory reporting.

RESULTS: From 1982 to 2015, a total of 670 postmarketing cases had been reported via pharmacovigilance, for an overall reporting rate of approximately one ADR per 3900 administered standard doses. Of these cases, 343 involved ADRs considered clinically relevant risks (33 thromboembolic complications, 97 inhibitor formation, 110 hypersensitivity or allergic reactions) or potential risks (103 suspected virus transmissions) for Humate-P. Most thromboembolic complications occurred in patients undergoing surgery or with other known risk factors. Inhibitor formation occurred mostly in patients with hemophilia A (24 cases were high titer). Most patients with hypersensitivity or allergic reactions had VWD. None of the reported suspected virus transmission cases were confirmed to be associated with Humate-P. Reported results of company-sponsored studies showed a low incidence of adverse events possibly or probably related to Humate-P.

CONCLUSIONS: More than 33 years of pharmacovigilance data continue to support the safety of Humate-P.

Hemophilia A and von Willebrand disease (VWD) are characterized, respectively, by deficiencies in Factor VIII (FVIII) and von Willebrand factor (VWF).¹ Historically, these conditions have largely been managed with clotting factor replacement therapy to restore hemostasis. Plasma-derived therapies have been associated with virus transmission, but since 1987 no transmissions have been confirmed.^{2,3}

Haemate-P/Humate-P (hereafter referred to as Humate-P) is a pasteurized human plasma-derived concentrate that contains both FVIII and a near-normal spectrum of VWF multimers.⁴ It was the first product developed to treat these disorders with a dedicated virus reduction step. It has a high proportion of high-molecular-weight VWF multimers known to be important in hemostasis compared with other commercially available FVIII and VWF concentrates; furthermore, the ratio of

ABBREVIATIONS: ADR(s) = adverse drug reaction(s); AE(s) = adverse event(s); DVT = deep vein thrombosis; HLT(s) = high-level term(s); ITI = immune tolerance induction; MedDRA = Medical Dictionary for Regulatory Activities; PE = pulmonary embolism; PT(s) = preferred term(s); SAE(s) = serious adverse event(s); SMQ(s) = standardized MedDRA query(-ies); VWD = von Willebrand disease.

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VWF to FVIII is approximately 2.4:1, allowing adjustment of VWF levels without raising FVIII to levels thought to be thrombogenic.⁵⁻⁷ The multimer profile in Humate-P is similar to that in normal plasma.⁶ Humate-P was developed by Behringwerke, which subsequently became part of CSL Behring. It was initially licensed in Germany in 1982 and subsequently approved in the United States in 1986 for the management of bleeding in patients with hemophilia A and later for VWD. Several publications have documented the efficacy of Humate-P in VWD and hemophilia A.^{4,8-13}

The manufacturing process for Humate-P includes multiple sequential steps that reduce the risk of virus transmission: 1) cryoprecipitation; 2) Al(OH)₃ adsorption, glycine precipitation, and NaCl precipitation; 3) heat treatment at 60°C for 10 hours in aqueous solution (i.e., pasteurization); and 4) lyophilization. Together, these processing steps achieve total cumulative virus reduction ranging from 6.0 to 11.7 log or more.¹⁴ Pasteurization is the most important step in this process because it is highly effective at inactivating a broad range of viruses that could potentially be present in plasma. The heat-labile FVIII molecule is stabilized during the heat treatment process by the addition of glycerin and sucrose. In 1988, citrate was replaced with antithrombin III and heparin in buffer solutions used during the purification process. This further enhanced stabilization of FVIII and increased yields.

Beyond disease transmission, thromboembolic complications are a concern with FVIII/VWF products, and inhibitor formation is a well-known risk in hemophilia A patients treated with FVIII concentrates. Furthermore, as with any biologic agent administered intravenously, hypersensitivity is a possibility.

Here, we reviewed the safety profile of Humate-P based on 33 years of spontaneous postmarketing reports of potential adverse drug reactions (ADRs) and the medical literature, with a focus on clinically relevant and potential risks associated with FVIII and VWF products. This review provides clinicians with essential safety data to inform the choice between Humate-P and newer recombinant factor products.

MATERIALS AND METHODS

Pharmacovigilance reporting

Reports of potential ADRs were compiled from the date of first marketing authorization (June 1982) to November 30, 2015, as part of routine pharmacovigilance at CSL Behring. The data included spontaneous ADR reports, reports of adverse events (AEs) from postmarketing trials and regulatory agencies (including US MedWatch), and AEs reported in the scientific literature. Details, including the date, country of origin, patient age and sex, indication,

Humate-P dose, concomitant blood products, manifestations, and event outcomes, were recorded for each report, if available. In addition, if the blood product was not specified, attempts were made to document which FVIII concentrates were used.

A narrative description of the case was obtained whenever possible. Follow-up information was queried when relevant information was missing from the initial report; however, missing information was not always available. The coding used for this analysis was the Medical Dictionary for Regulatory Activities (MedDRA, Version 18.1). ADRs were classified as serious or nonserious according to the standard definition of a serious event (i.e., an event that resulted in death, was life-threatening, required hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was medically important).

The total quantity of Humate-P distributed worldwide, including the United States, was determined from CSL Behring commercial records (data were only available since 1990). The exact number of patients administered Humate-P during the reporting period is not known; therefore, the following assumptions were made to calculate patient exposure: for long-term prophylaxis in patients with severe hemophilia A, the usual dose of Humate-P ranges from 20 to 40 international units (IU) per kilogram of body weight, given at conservative intervals of two or three times weekly. Based on a mean body weight of 70 kg and using a dose of 30 IU, this equates to an estimated standard dose of approximately 2100 IU (rounded down to an estimated dose of 2000 IU based on the vial presentations). Assuming that this dose is given twice weekly (particularly for prophylaxis in severe VWD), an annual dose equates to approximately 208,000 IU per patient, representing approximately 25,000 patient-years of exposure.

A detailed review was performed on ADRs considered to be clinically relevant during use of Humate-P (i.e., thromboembolic complications, FVIII or VWF inhibition, hypersensitivity or allergic reactions) or those that were potential risks (i.e., suspected virus transmission). These cases were identified using standardized MedDRA queries (SMQs), high-level group terms, high-level terms (HLTs), and preferred terms (PTs) within the MedDRA dictionary. Thromboembolic complications were identified in the pharmacovigilance database using the SMQs “embolic event” or “thrombotic event” (narrow). FVIII or VWF inhibition was identified using the SMQ “lack of efficacy/effect” (narrow), as well as the specified PT inhibitor or antibody development (including the PTs FVIII inhibition, inhibiting antibodies, and VWF inhibition). Hypersensitivity or allergic reactions were identified using the SMQ “hypersensitivity” (narrow), which included anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, hypersensitivity, angioedema, and related terms.

Suspected virus transmission was identified in the database using the high-level group term “viral infectious disorder”; the HLT “infectious transmission”; the HLT “virus identification and serology”; or PTs associated with hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), parvovirus, cytomegalovirus, and Epstein-Barr virus.

Each identified case underwent a medical assessment to confirm that it met the case definition of either an important or potential risk. The remaining cases not considered to be clinically significant risks for analysis were summarized as a group.

Literature review

Literature searches were conducted using Embase and PubMed. The goal was to identify original, English language articles published between January 1, 1980, and November 18, 2015, that reported on Humate-P and blood clotting FVIII inhibitor or thromboembolism or allergic reaction/hypersensitivity or virus transmission. For Embase, the following search strategy was used: Humate-P or Haemate-P or Haemate and thromboembolism or “embolism and thrombosis” or virus transmission or disease transmission or “allergic reaction” or hypersensitivity or inhibition or inhibitor or (infection or viruses or virus or viral and transmission). For PubMed, we used the following search terms: Haemate-P or Humate-P or Haemate and “embolism and thrombosis” or allergic reaction or “factor VIII/antagonists and inhibitors” or inhibition or inhibitor or (viral or virus or viruses or infection* and transmission).

Once relevant publications were identified, the authors, methods, and periods were examined to eliminate any duplicate data from multiple reports. Data were extracted from these reports regarding the number and age of patients infused with Humate-P, the specific type of VWD deficiency and indication, the treatment regimen, and the occurrence of AEs, including their reported relation to Humate-P. Only reports with safety data were included, and all reported AEs were included in the analysis regardless of whether a relation to Humate-P could be established.

RESULTS

Pharmacovigilance

The cumulative quantity of Humate-P distributed worldwide since 1990 is more than 5.2 billion IU, corresponding to approximately 2.6 million standard doses and approximately 25,000 patient-years of exposure. During the reporting period from 1982 to 2015, our analysis showed that 670 postmarketing ADR cases were reported, corresponding to an overall reporting rate of one ADR per 3900 administered standard doses. The mean age of patients

was 24.6 years, ranging from less than 1 to 91 years. Of the 670 cases, 249 occurred in females and 353 in males (68 cases did not have sex recorded); 13 were reported to have a fatal outcome, none of which was related to administration of Humate-P (Table 1). Overall, 343 ADRs represented a clinically relevant risk of Humate-P therapy (including 33 cases of thromboembolic complications, 97 cases of inhibitor formation, and 110 cases of hypersensitivity or allergic reactions), and 103 were cases of suspected virus transmission.

Thromboembolic complications

Thromboembolic complications are a concern because they could result from elevation of FVIII levels. As shown in Table 2, 33 cases were reported in patients treated with Humate-P; this is approximately one case per every 78,787 standard doses administered. In five cases, the brand of FVIII and VWF concentrate was unknown. Mean age was 48 years (range, 5-84 years) with two patients not more than 12 years of age; 19 patients were female, and 14 were male. There were 20 cases of deep venous thrombosis (DVT) and pulmonary embolism (PE), three cardiac-related thrombosis cases (i.e., coronary artery occlusion and acute myocardial infarction), three transient ischemic attacks or stroke cases, and seven cases with “other” thrombotic complications (Table 2). Twenty-four of these ADRs occurred in VWD patients, six occurred in patients with hemophilia A, one of whom was receiving immune tolerance induction (ITI). For the remaining three cases, the indication was unknown. In 19 cases, the ADR was associated with surgery, which is a known independent risk factor for DVT or PE. From the available information in these reports, most patients did not receive heparin-based thromboprophylaxis. Further reported independent risk factors for DVT or PE were angiodysplasia ($n = 1$), monoclonal gammopathy ($n = 2$), and cancer ($n = 3$). Additionally, there was a thromboembolic complication in one patient who received a higher-than-prescribed dose.

Inhibitor formation

Inhibitor formation is a well-known risk in hemophilia A patients treated with FVIII concentrates and has also been described generally in Type 3 VWD patients.¹⁵⁻¹⁷ Upon medical review, 97 reports of inhibitor formation were identified in the Humate-P pharmacovigilance database: 69 cases of FVIII inhibitors and 28 cases of VWF inhibitors (Table 3 and Table 4). This is approximately one case per 26,804 standard doses. In 33 cases, it was unknown whether Humate-P was used. Among patients with inhibitor formation, the mean age was 18.3 years (range, 0.7 months to 74 years), and 25 patients were not more than 2 years of age. Sixty-nine cases of FVIII inhibitors were reported, including two reported as acquired hemophilia and another with an unknown indication; in 24 cases, the inhibitor was described as high titer (Table 3). There were

TABLE 1. Fatal reports

Case	Year	Diagnosis	Cause of death	Age (years)	Sex	Other medication information
1	1987	Hemophilia A	HIV AIDS	24	Male	On clotting factor not virus inactivated from 1979. Later used products of various manufacturers. Humate-P used in 1985.
2	1988	Hemophilia A	HIV AIDS	21	Male	On clotting factor not virus inactivated from 1970. Humate-P possibly administered in 1984. Positive for HIV in 1985.
3	1989	Hemophilia A	HIV AIDS	9	Male	On clotting factor, Humate-P and another product from another manufacturer. Positive test for HIV in 1985.
4	1990	Acquired FVIII inhibitor	Hepatitis B	Unknown age	Female	Recent vapor heat-treated FVIII from another manufacturer as well as Humate-P and FEIBA. One year after starting treatment, hepatitis test was positive. Physician attributed hepatitis to other manufacturer's product. Also received immunoglobulin, with RBCs not subject to virus reduction.
5	2002	Angiodysplasia, acquired VWD, monoclonal gammopathy of unknown significance	Gastrointestinal bleeding	76	Female	Also received whole blood. Risk factor for DVT included femoral vein catheter. Complicated course with death unrelated to Humate-P.
6	2008	VWD	Sepsis	37	Female	Post-gastric bypass surgery during which Humate-P was used. Death unrelated.
7	2010	Hemophilia A	HIV AIDS, hepatitis C	48	Male	Recent multiple FVIII products, both virus inactivated and not inactivated as well as Humate-P.
8	2010	Sepsis, multiorgan failure, DIC	Multiorgan failure, TRALI, shock	14	Male	Hemorrhage, septic shock, complicated case with heart failure. Treated with Humate-P plus multiple other products for bleeding.
9	2013	Hemophilia A; ITI for inhibitor	Dyspnea, hemoptysis, cardiac failure, PE	5	Male	Unknown which FVIII product used; multiple other products used, including recombinant FVIIa.
10	2014	Aortic dissection	Postsurgery, had been treated with dabigatran, died of hemorrhagic shock	76	Male	Multiple blood and coagulation factors used, including Humate-P.
11	2014	Hemophilia A	Hemorrhagic shock, ARDS	53	Male	Hematemesis thought to be due to esophageal varices, developed hemorrhagic shock, ARDS during treatment with multiple blood products including Humate-P.
12	2015	VWD Type 3	Hypoglycemia, unexpected sudden death	52	Female	Death not related to Humate-P.
13	2015	Unknown	HIV AIDS, hepatitis C	32	Male	Outpatient fistula surgery; 1 day later suddenly died after dialysis; had episode that day of hypoglycemia. Son reported 1986 death in 2015. Not known what products were used.

AIDS = acquired immunodeficiency syndrome; ARDS = acute respiratory distress syndrome; DIC = disseminated intravascular coagulation; TRALI = transfusion-related acute lung injury.

TABLE 2. Thrombotic complications

Case	Category	Reported indication	Case event	Coexisting condition	Age (years)	Sex	Additional information
1	DVT/PE	VWD Type 1	PE	Hysterectomy	37	Female	PE fourth day after hysterectomy.
2	DVT/PE	Hemophilia A	DVT	Osteotomy	67	Male	Heparin use resulted in compartment syndrome, not known if Humate-P used.
3	DVT/PE	VWD Type 2M	DVT	Vulva cancer; monoclonal gammopathy	81	Female	DDAVP used.
4	DVT/PE	VWD	PE	Cholecystectomy	49	Female	Also treated with tranexamic acid and Premarin, higher dose of FVIII than needed.
5	DVT/PE	VWD Type 1	DVT, PE	Arthroscopic knee surgery	56	Female	4 days postsurgery.
6	DVT/PE	VWD Type 1	DVT	Surgery (colostomy)	22	Female	
7	DVT/PE	VWD	PE	Knee replacement; obesity	75	Female	
8	DVT/PE	VWD acquired	DVT	Monoclonal gammopathy	76	Female	Died of GI bleeding.
9	DVT/PE	VWD Type 3	PE, DVT	angiodyplasia	53	Female	
10	DVT/PE	VWD	PE, DVT	Hepatocellular carcinoma	27	Male	PE developed 6 days after first dose.
11	DVT/PE	Hemophilia A severe	Old DVT and postthrombotic swelling	Varicose vein ligation	14	Male	Older thrombosis identified with postsurgery swelling.
12	DVT/PE	VWD Type 2	PE	Ankle fracture in screw fixation	63	Female	
13	DVT/PE	VWD acquired	DVT	Foot operation, old pulmonary embolic disease	13	Male	
14	DVT/PE	VWD Type 2N	PE	Hip surgery, obesity	72	Male	2 days after surgery.
15	DVT/PE	VWD Type 1	PE	Total hip replacement	56	Male	Overdose of Humate-P given erroneously.
16	DVT/PE	Unknown	PE	Surgery		Female	
17	DVT/PE	Hemophilia A severe; high-titer inhibitor	PE	ITI	5	Male	Fatal outcome; not known if Humate-P used.
18	DVT/PE	VWD	DVT	Dental surgery with tranexamic acid during pregnancy		Female	Humate-P not confirmed.
19	DVT/PE	Unknown	PE	Surgery for colon cancer	77	Female	Not known if Humate-P used.
20	DVT/PE	VWD	DVT; catheter thrombosis	Gastric carcinoma	84	Female	Also received tranexamic acid.
21	Cardiac	VWD	Coronary graft occlusion	Coronary artery disease	60	Female	Post-bypass surgery.
22	Cardiac	VWD Type 2A	Acute MI, occlusion left anterior descending artery	Hypertension, angiodysplasia, also on Vlla	50	Male	Recovered.
23	Cardiac	Hemophilia A severe	Acute MI	Knee replacement	63	Male	Not known if Humate-P used.
24	TIA/stroke	VWD	TIA	Prostate biopsy	65	Male	30 min postinfusion had neurologic defect and hemiparesis on right, recovered 1 day later.
25	TIA/stroke	VWD	TIA	Mastectomy, also received Stimite	51	Female	Recovered.
26	TIA/stroke	Hemophilia A severe with inhibitor	Stroke, carotid arterial stenosis	ITI, hydrocephalus	1	Male	Complex medical history, resolved with sequelae.
27	Other	VWD Type 3	Central retinal vein thrombosis	Oral contraception, target joint	40	Female	
28	Other	VWD	Mesenteric and splenic vein thrombosis	Tranexamic acid and inflammatory bowel disease	61	Male	

Table 2: Continued

Case	Category	Reported indication	Case event	Coexisting condition	Age (years)	Sex	Additional information
29	Other	VWD	Thrombosis hemorrhoid vein	Perineal swelling and anal fissure, sphincterectomy, bladder spasms, and difficulty urinating	50	Female	Thrombosis 9 days after surgery.
30	Other	Unknown	Catheter occlusion	Iron replacement	70	Female	Recovered.
31	Other	Hemophilia A with inhibitor	Venus port occluded; catheter occlusion	ITI	12	Male	
32	Other	VWD acquired	Clot in left ventricular assist device	Post-abdominal aortic aneurysm repair	61	Male	Recovered.
33	Other	VWD	Catheter occlusion		74	Female	

GI = gastrointestinal; MI = myocardial infarction; TIA = transient ischemic attack.

28 reported cases of inhibitor formation in patients with VWD (Table 4), with 12 of these patients being female. VWF inhibitors occurred mostly in patients with Type 3 VWD. In six cases, the patient had an associated allergic reaction to the drug.

Hypersensitivity or allergic reactions

Upon medical review, 110 cases related to hypersensitivity or allergic reactions were identified in the Humate-P pharmacovigilance database. This is approximately one case per 23,636 standard doses. The mean age of patients was 32 years (range, 1.7 months-76 years), and 10 patients were not more than 2 years of age. Most patients (64%) had VWD. Events included hypersensitivity (n = 51), anaphylactic reaction (n = 22), anaphylactic shock (n = 3), anaphylactoid reaction (n = 5), and angioedema (n = 4).

Nineteen of the reported anaphylactic reactions were serious; three of these did not have sufficient details reported to assess a possible relation to Humate-P. Among the three reported patients with anaphylactic shock, the brand of concentrate was unknown in one case and the clinician did not feel the reaction was due to Humate-P in another case. For the remaining hypersensitivity cases, a range of ADRs was reported: urticaria (n = 40), edema (n = 20), asthma and/or wheezing or bronchospasm (n = 20), and impact on the larynx and thus breathing (n = 10). Based on medical review, six cases were identified that were also associated with inhibitor formation (see details in Table 2 and Table 3). Many of the hypersensitivity and anaphylactic cases also reported reactions to other FVIII products or other drugs, and the patients had other allergies.

Suspected virus transmission

Cases of suspected virus transmission are thoroughly followed up with the reporting physician, and, if lot numbers are available, investigation of concerned batches or related plasma pools will occur. We identified 103 cases of potential virus transmission using the PTs associated with hepatitis A, B, and C; HIV; parvovirus; cytomegalovirus; and Epstein-Barr virus. Mean age was 27.3 years (range, 2.3-54 years), and one patient was not more than 2 years of age. Of these, 22 patients were female, and 66 were male (15 cases did not report sex).

Fifty-nine cases of potential transmission of hepatitis C were reported. Of these, four cases could not be finally assessed due to insufficient information. In the remaining cases, the use of other plasma-derived products before the introduction of viral inactivation or the use of other blood products not subject to virus reduction steps were the more likely cause of the infection. Also, there was insufficient information to determine whether transmission occurred by modes other than transfusion. There were 17 reports of hepatitis B, three of hepatitis A, and eight of parvovirus infection. A direct link to Humate-P

TABLE 3. Inhibitor to FVIII

Case	Country	Reported indication	Case event	Coexisting condition	Age (years)	Sex	Additional information
1	Germany	HA	High-titer inhibitor	Hepatitis C	2	Male	ITI and FEIBA.
2	Switzerland	HA severe	High titer	Elbow hemarthrosis	39	Male	High responder inhibitor after long-term Humate-P.
3	Austria	HA	Temporary nonresponse	Hematoma of thorax and rib fractures	51	Male	Inhibitor disappeared after 2 months.
4	Germany	HA	High titer	Arthropathy	26	Male	Multiple products; less pronounced with Humate-P than others.
5	Germany	HA severe	High titer		12	Male	Successfully treated ITI with Humate-P. Multiple products.
6	Germany	HA mild	High titer (26 BU)		14	Male	Multiple products but inhibitor said to develop after Humate-P.
7	Germany	HA mild	High-titer inhibitor		74	Male	Not known if he had inhibitor in past.
8	Germany	HA	High-titer inhibitor	Epidural hematoma	0.7	Male	Treated with ITI successfully.
9	Germany	HA	Transient high-titer inhibitor		16 months	Male	Received recombinant product and treated with ITI successfully.
10	Germany	HA	High-titer inhibitor	Intron 22 inversion	15	Male	ITI; inhibitor developed on recombinant product.
11	Germany	HA moderate	Inhibitor	Appendectomy	14	Male	Multiple allergies; other products involved.
12	Germany	HA severe	High-titer inhibitor (11.7 BU)	Adenoidectomy	3	Male	Large volume of Humate-P.
13	Germany	HA mild	Inhibitor (14 BU)	Resection for urethral carcinoma; Exon 14 mutation	74	Male	
14	Sweden	HA	Inhibitor		1	Male	Primarily treated with recombinant product (one dose of Humate-P).
15	Spain	HA	High-titer inhibitor	Exon 14 insertion	13 months		Recently received Advate which was probable cause of inhibitor.
16	Germany	HA severe	High-titer inhibitor	Intron 22 inversion	20 months	Male	Switched product for ITI.
17	Germany	HA	Low-titer inhibitor	Intron 22 inversion	15 months	Male	
18	Germany	HA	Inhibitor (max 4 BU)	Intron 22 inversion	13 months	Male	Treated with ITI successfully.
19	Germany	HA	High-titer inhibitor		29 months	Male	ITI then continued Humate-P.
20	Germany	HA	High-titer inhibitor	Exon 25 stop mutation	3	Male	ITI then continued Humate-P.
21	Germany	HA	High-titer inhibitor		5	Male	ITI.
22	Germany	HA	Low-responder inhibitor	Intron 22 inversion	18 months	Male	ITI with no further inhibitor.
23	Germany	HA severe	High-titer inhibitor	Stop mutation	16 months	Male	ITI and treated with FEIBA and FVlla.
24	Germany	HA	Inhibitor	Surgery			Had ITI with Humate-P.

Table 3: Continued

Case	Country	Reported indication	Case event	Coexisting condition	Age (years)	Sex	Additional information
25	Germany	HA severe	Low-responder inhibitor	Nonsense mutation	66	Male	Treated with ITI successfully.
26	Germany	HA	High-titer inhibitor		13 months	Male	ITI not successful. Treated with ITI. Also received recombinant factor.
27	Austria	HA	High-titer inhibitor	Large gene deletion	3	Male	
28	Germany	HA	High-titer inhibitor	Intron 22 inversion	15 months	Male	
29	Canada	HA	FVIII inhibitor		18 months	Male	
30	Austria	HA mild	High-titer inhibitor	Retroperitoneal hematoma; Exon 22 missense mutation; Exon 14 polymorphism	51	Male	Inhibitor disappeared.
31	Germany	HA severe	High-titer inhibitor		49	Male	ITI.
32	Germany	HA	Low-titer inhibitor	Traumatic bleeding, pseudo-tumour erosion into colon	18 months	Male	
33	United States	HA	High-titer inhibitor	Family history of inhibitor	9	Male	Inhibitor disappeared with steroids.
34	Germany	HA	High-titer inhibitor	Gene mutation C.797G7A	67	Male	
35	Germany	HA	Mild transient inhibitor	Pancreaticoduodenostomy	57	Female	Death after multiple complications; Humate-P given due to low FVIII before inhibitor identified.
36	Germany	HA acquired					Humate-P not adequate.
37	United States	HA acquired	Acquired inhibitor	Sickle cell disease; post-stem cell transplant	44	Male	
38	United Kingdom	Indication not known	Prior anaphylactic reaction; subsequent inhibitor		20	Female	
<i>Cases with unknown Humate-P use</i>							
1	Germany	HA	Transient inhibitor	Small deletion	7 months		
2	Germany	HA	Transient inhibitor	Intron 22 inversion	3.5		
3	Germany	HA	Low-titer inhibitor	Intron 22 inversion	5.5		
4	Germany	HA	High-titer inhibitor	Missense mutation	8		
5	Germany	HA	Low-titer inhibitor	Missense mutation	11		
6	Germany	HA			19		
7	Germany	HA mild	High-titer inhibitor	Null mutation	35		
8	Germany	HA mild	High-titer inhibitor		57	Male	Four exposures to some product.
9	Czech Republic	HA	High-titer inhibitor				
10	Germany	HA	Unknown inhibitor	Intron 22 inversion	8 months	Male	ITI.
11	Germany	HA	High titer		4	Male	
12	Germany	HA	Low-titer inhibitor		6	Male	FVIII treatment successful.
13	Turkey	HA	High-titer inhibitor	Septic arthritis	15	Male	Treated with recombinant Vlla.
14	Serbia	HA severe	High-titer inhibitor				
15	Poland	HA	High-titer inhibitor		28	Male	
16	Poland	HA	High-titer inhibitor		40	Male	
17	United Kingdom	HA	Low-titer inhibitor	Head injury	9 months	Male	ITI.
18	United States	HA		Total knee replacement; pseudotumour	35	Male	ITI used.

Table 3: Continued

Case	Country	Reported indication	Case event	Coexisting condition	Age (years)	Sex	Additional information
19	United States	HA	High-titer inhibitor	Arthropathy	13 months	Male	
20	Poland	HA	High-titer inhibitor		3	Male	Successful ITI FVIIa.
21	Poland	HA	High-titer inhibitor		23	Male	Treated with FVIIa successfully.
22	Turkey	HA severe	Inhibitory antibodies to FVIII		7	Male	
23	Germany	HA	Inhibitor	Intron 22 inversion	1	Male	ITI successful.
24	United States	HA	FVIII inhibitor		14	Male	ITI used.
25	Italy	HA		Iliopsoas hematoma	60	Male	
26	United States	HA moderate	FVIII inhibitor		40	Male	
27	United States	HA moderate	High-titer inhibitor	Right hip replacement	44	Male	
28	United States	HA moderate	Inhibitor	Muscle hematoma	7	Male	
29	Germany	HA severe	High-titer inhibitor	Intron 22 inversion	10 months	Male	Treated with ITI successfully; later FEIBA.
30	Denmark	HA	Inhibitor	TUR of prostate	71	Male	VII as treatment.
31	United States	HA	High-titer inhibitor	Ankle hemorrhage	6	Male	Treated with recombinant VIIa.

BU = Bethesda unit; HA = hemophilia A; TUR = transurethral resection.

could be excluded based on available laboratory data, evidence regarding the patient's medical history, or a negative polymerase chain reaction test for the concerned batches or the available information was inadequate to form any conclusion. There was one case of cytomegalovirus and two cases of Epstein-Barr virus infections in which no other cause could be found; these are white blood cell-associated viruses not transmitted by plasma-derived products.¹⁸ There were 24 cases of HIV infection, but other causes of infection were identified in all cases. In all cases of suspected virus transmission (except the ones with insufficient information), the causal relation to the product was assessed as unlikely. Among all reports of infections, 33% had used other products or had other causes identified; 31% had received clotting factor products before the introduction of virus reduction steps in manufacturing; 11% had received blood products not subject to virus reduction steps such as red blood cells (RBCs), platelets, or plasma; and 26% had insufficient information or a timing of the infection that did not correlate with Humate-P administration. To date, no confirmed cases of viral or prion transmission have been associated with Humate-P.

Other reported events

To analyze the overall safety profile of Humate-P, all 670 cases were reviewed by respective MedDRA system organ classes, including the 346 cases classified as hypersensitivity, inhibitor, thromboembolic, or viral related. In total, 1730 ADRs were reported (one case could report more than one ADR): most of the ADRs were categorized under general disorders and administration site conditions (266), investigations (221), and skin and subcutaneous tissue disorders (192). In addition to the ADRs associated with the important or potential risks of Humate-P, the most common MedDRA PTs reported (≥ 30) were nausea, chills, drug ineffective, pyrexia, dyspnea, and pruritus (Fig. 1). Among the 37 reports of drug ineffective, three cases also included reports of inhibitors. There was also one case of hemolytic anemia thought to be related to an antibiotic and one case of thrombocytopenia with uncertain relation to Humate-P.

Literature reports

In 2009, Federici⁹ reviewed the safety profile of clotting factor concentrates and described the most common AEs as (1) fever, hypersensitivity, and allergic or anaphylactic reactions; 2) inhibitor formation; 3) thromboembolic events; and 4) blood-borne infections. The authors stated that fever, hypersensitivity, and allergic or anaphylactic reactions were observed only rarely with all clotting factor concentrates and that these types of reactions are a potential concern with any plasma-derived protein. Inhibitors were noted to be rare in VWD compared with hemophilia

TABLE 4. Inhibitor to VWF

Case	Country	Reported indication	Case event	Coexisting condition	Age (years)	Sex	Relevant medical history
1	Switzerland	VWD	Temporary nonresponse	Synovectomy right knee	8	Female	Nonresponse temporarily due to inflammation.
2	Italy	VWD Type 3	Immune reaction accompanied by inhibitors	Dental extraction	23	Male	Reaction to multiple products.
3	Romania	VWD	Nonresponse to product; inhibitor levels not reported	Amputation with bleeding	28	Male	Humate-P plus blood products including cryoprecipitate.
4	Netherlands	VWD Type 3	Low recovery; shortened half-life		51	Female	
5	Spain	VWD	Low-titer inhibitor (1.5 BU)	Dysmenorrhea; ovarian follicle rupture	22	Female	ITI with another product.
6	United States	VWD 2N	Inhibitor suspected	Surgery	58	Male	Lab tests negative for inhibitor.
7	Germany	VWD Type 3	Allergic reaction; questionable inhibitor	Prothrombin mutation	36	Female	Also reacted to other brands.
8	Germany	VWD Type 3	High-titer inhibitor (2.4 BU) associated with allergic reaction		18	Male	
9	Germany	VWD Type 3	High-titer inhibitor		10 months	Male	Subsequently had ITI.
10	Greece	VWD	Severe inhibitor	Prostate cancer biopsy; radiotherapy led to bleeding	>62	Male	Required IVIG and transfusions.
11	Germany	VWD Type 3	Severe inhibitor	Joint bleeding	6	Female	ITI with Humate-P; recurrence of antibody; healed with Vlla and tranexamic acid.
12	Germany	VWD Type 3	High-titer anti-ristocetin antibody		7	Female	ITI.
13	Canada	VWD Type 3	High-titer inhibitor	Postcircumcision bleeding, head injury	15 months	Male	Initially treated with recombinant factor; ITI successful.
14	Portugal	VWD Type 3	Clinical nonresponder		Adolescent	Male	Antibody against VWF not confirmed.
15	Greece	VWD Type 3	High titer inhibitor to FVIII; VWF inhibitor not detected	Joint bleeding; inflammation; KFH	8	Male	Other drugs used.
16	United Kingdom	VWD Type 3	VWD inhibitor		2	Female	Changed to Vlla.
17	Spain	VWD Type 3	VWD inhibitor suspected	Pregnant	30	Female	Treated with Vlla and another FVIII/VWF drug.
18	United Kingdom	VWD Type 3	VWD inhibitor	Epistaxis	5	Female	ITI and subsequent successful use of Humate-P.
19	United Kingdom	VWD Type 3	Possible VWF inhibitor		3	Male	Switched to another product.
20	Netherlands	VWD	VWF inhibitor with allergic reaction	Pregnant; uterine atony; placenta abruptio	34	Female	
21	United Kingdom	VWD	Inhibitor to FVIII and VWF and allergic reaction	Epistaxis	32	Male	Also allergic reaction to other FVIII/VWF products.
22	United States	VWD	VWF inhibitor	Anaphylaxis			Also reacted to other brands.
23	United States	VWD	VWF inhibitor	Anaphylaxis			
24	Portugal	VWD Type 3	VWF inhibitor		8	Male	
25	United States	VWD	VWF inhibitor	Allergic reaction	2		Also reacted to other brands.
26	United States	VWD Type 3	VWF inhibitor	IgE hypersensitivity	8		Also reacted to other brands.
<i>Humate-P use unknown</i>							
1	Portugal	VWD Type 3	Suspected inhibitor; poor response to product	Ovarian cysts	19	Female	
2	Germany	VWD Type 3	VWF inhibitor	Surgery	4	Female	Responded to recombinant Vlll.

BU = Bethesda unit; KFH = Kaposiform hemangioendothelioma.

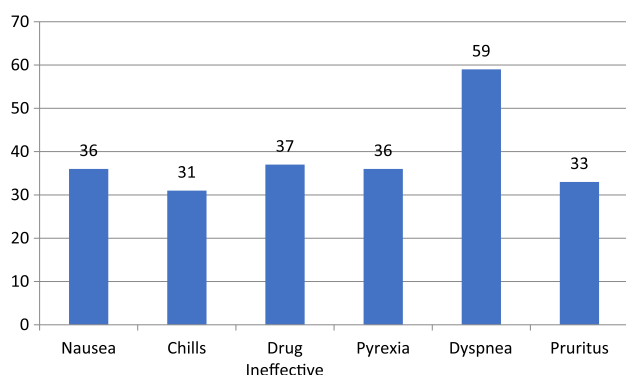


Fig. 1. Most common (≥ 30 events) other reported events by MedDRA PT. [Color figure can be viewed at wileyonlinelibrary.com]

and generally limited to Type 3 patients with a large gene deletion. Regarding thromboembolic events, the authors indicated that sustained high plasma levels of FVIII may increase the risk of thrombosis. They suggested that patients be monitored to avoid values more than 150 IU/dL and that anticoagulation with low-molecular-weight heparin might be reasonable. With available technology in use at that time, the authors estimated that the risk of blood-borne infection is “virtually zero.” More recently, the VWD International Prophylaxis Study Group presented retrospective data on VWF and FVIII concentrate prophylaxis in patients with VWD. Data were presented on 59 patients, most of whom were Type 3, and Humate-P was used in 77% of cases. There were no cases of thromboembolism reported.¹⁹ Another study of continuous infusion of clotting factor concentrates that included Humate-P, among other products, reported no AEs in 46 patients.²⁰

Reports of thromboembolic events occurring in other published studies have been captured in our reported ADRs and analyzed.^{14,21} In addition, our ADR database captured three reports of transient neutralizing antibodies developing in VWD patients receiving prophylaxis with Humate-P and a report of anaphylactoid reactions to both Humate-P and Willate.²²⁻²⁴ Initial studies confirmed that Humate-P does not transmit hepatitis B, and later it was shown that it also does not transmit either hepatitis C or HIV.^{4,25}

Sponsored studies

Several company-sponsored studies have assessed the safety profile of Humate-P. A large retrospective study conducted by the Canadian Hemophilia Centers reported the safety profile of Humate-P in 97 Canadian patients with VWD.^{8,11} These patients had 73 surgeries, 344 separate bleeding events, and 93 other events (e.g., test doses or invasive procedures) and received 20 cycles of prophylactic treatment with Humate-P. Four patients (4%)

experienced seven nonserious AEs that were considered possibly or probably related to Humate-P, including chills, phlebitis, vasodilation, paresthesia, pruritus, rash, and urticaria. One serious adverse event (SAE) was an accidental injury resulting in death that was not related to treatment. In 2003, a prospective, multicenter, open-label, nonrandomized study of Humate-P in VWD reported 24 AEs in 10 patients receiving 53 treatments for urgent bleeding.¹⁰ Two SAEs (menorrhagia with anemia and hemorrhage) were considered unrelated to treatment. Of the remaining SAEs, one was considered related to treatment (a mild allergic reaction that was repeated on retreatment). The same study group also reported on 39 VWD patients requiring urgent surgery who received Humate-P.¹³ In this prospective, multicenter, open-label, nonrandomized trial, 55 AEs were reported in 24 of 42 surgeries. Eight AEs were considered possibly related to Humate-P, including paresthesia (two events), allergic reaction, vasodilation, peripheral edema, extremity pain, pseudo-thrombocytopenia, and pruritus. The case of pseudo-thrombocytopenia resulted in discontinuation of Humate-P. A study of Humate-P in VWD patients undergoing elective surgery was reported by the European Humate-P Study Group in 2007.²⁶ Five AEs reported in five patients during the perioperative period were possibly related to Humate-P. These included PE, thrombophlebitis, vomiting, rash, and increased alanine aminotransferase level. The PE developed after bilateral knee replacement in an 81-year-old female with Type 1 VWD and was considered serious. Despite other risk factors, she had not received any thromboembolic prophylaxis. Her FVIII level reached 450 IU/dL. The other AEs were mild in severity.

In 2011, the results of another prospective, open-label elective surgery study, conducted at 15 US and two European centers, were published.²⁷ Among 42 patients in the safety population, 35 had their planned surgery. Three patients experienced AEs in the pharmacokinetic phase and 30 (86%) during the surgical phase. There were seven SAEs, including vaginal bleeding, gastrointestinal bleeding after bariatric surgery, cerebral hemorrhage, and subdural hematoma, that were related to either ineffective hemostasis or, in the case of cerebral hemorrhage, unexpected bleeding despite effective surgical hemostasis. Two other SAEs (sepsis and pyelonephritis) were considered unrelated to treatment. Other commonly reported AEs were nausea (37%), constipation (14%), dizziness (14%), pain (14%), fever (11%), hemorrhage (11%), pruritus (9%), abdominal pain (9%), chest pain (9%), and urinary retention (9%). Six AEs were considered possibly related to Humate-P, including headache ($n = 3$), itching ($n = 1$), nausea ($n = 1$), and dizziness, which were all mild in severity and self-limiting except for one individual who complained of nausea for 30 days.

Recently, Miesbach and colleagues¹² reported on a 25-year retrospective observational study of Humate-P in 71 VWD patients. They observed no allergies or transmission of viral infections and only one adverse reaction, a case of PE attributed to incorrect dosing (due to transcription error, the patient received three times the desired dose).

An interim analysis from a prospective, long-term (4 years), observational, pharmacovigilance study of Humate-P in 108 patients (101 with VWD and seven with hemophilia A) showed that one African American hemophilia patient developed a low-titer inhibitor that was successfully eliminated by ITI. There were no reported cases of thromboembolic events or viral transmission.^{28,29} In a small study of ITI with Humate-P, no AEs were reported among the three patients treated.³⁰

DISCUSSION

This article reviews the safety of Humate-P based on 33 years of pharmacovigilance. Humate-P was initially widely used for treating hemophilia A, but, in recent years, it has been used more for VWD. Humate-P has the distinction of being on the market longer than any other product for the treatment of bleeding disorders.

Pharmacovigilance is based not only on voluntary reporting of potential adverse reactions by physicians and others but also on follow-up of all reports in clinical trials and the medical literature. It encompasses collection and assessment of safety data from all sources. While the voluntary reporting system has the disadvantage of depending on a physician's and patient's willingness to report ADRs, not all reported events are confirmed to have a causal relation to the drug, indicating that in fact a wide net has been cast. We must, however, concede that ADRs are historically underreported.³¹ However, SAEs are more likely to be reported.³² In addition, in the past 15 years, additional post-marketing studies with Humate-P have been performed for marketing authorization in the United States.^{8,10,11,13,26} In these trials, all AEs were captured prospectively as opposed to ADRs in spontaneous reporting. This coincides with the evolution of pharmacovigilance to a more proactive approach to identify safety signals with additional regulatory initiatives by the US Food and Drug Administration (sentinel system) and European Medicines Agency.^{32,33}

The risk of thrombosis in treated patients relates to elevated FVIII in addition to other comorbidities.^{34,35} The pharmacovigilance data show that, compared with the overall number of treated patients, only a small number of thromboembolic events occurred, with most associated with ITI, surgery, or other prothrombotic conditions. Gill and Mannucci³⁶ addressed the concern related to the risk of thromboembolic events in those with high levels of VWF or FVIII. They indicated that there is no evidence suggesting the risk of thromboembolic complications is significantly different between the various commercially

available products. Furthermore, the authors indicated that many VWD patients treated with concentrate will develop high levels of FVIII and/or VWF, but most will not suffer thromboembolic complications. One could speculate that Humate-P with the lowest relative FVIII content should have a lower risk of thrombosis. Nevertheless, they support current guidelines recommending that VWD patients have their FVIII and VWFR:RCo levels monitored daily while being treated with VWF or FVIII concentrates for surgery. In addition, routine thromboprophylaxis should be considered, particularly if other prothrombotic conditions are present.

Pharmacovigilance reports of inhibitors or hypersensitivity are relatively low for intravenously administered and FVIII or VWF products, whether plasma derived or recombinant. A recent randomized study of plasma-derived FVIII concentrate versus recombinant FVIII showed a much lower rate of inhibitor formation with plasma-derived products.³⁷

To date, there have been no confirmed reports of disease transmission with Humate-P. Not all cases reported sufficient detail for a thorough assessment, but, in most cases, other more likely possible causes of transmission were identified. Had there been a breakdown in the virus inactivation of Humate-P, one would have expected a cluster of cases in a particular batch. Pharmacovigilance data are checked for such incidents, and no clusters have been detected for Humate-P.

A limitation of this review is that, in many cases, the administered FVIII/VWF product could not be identified. If the report came from a country in which Humate-P was marketed, the process obligates the clinical safety or pharmacovigilance group to follow-up on ADR reports when the brand of FVIII or VWF was unknown or not specified. In some cases, patients were treated with more than one brand of product, and it was impossible to determine which product was related to the ADR.

Postmarketing safety studies such as the one reported here collect data on patients who would not ordinarily be included in clinical trials, rare events, and provider concerns. The additional data from these studies are becoming more frequently reported by other companies³³ and us.³⁸

We have confirmed the relative safety profile of Humate-P and estimate the rate of thromboembolic events, inhibitor formation, and hypersensitivity reactions at approximately one in 15,476 cases or 101 patient-years. Humate-P has proven, through more than 30 years of clinical experience, to have a remarkable safety record that should be considered when making product choices for patients with hemophilia A or VWD.

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CONFLICT OF INTEREST

PK has served on a yearly advisory board for CSL Behring receiving an honorarium. He has received speaking fees from Octapharma and Baxalta in the past year. KWH, AS, HM, and TS are employees of CSL Behring.

REFERENCES

1. Leebeek FW, Eikenboom CJ. Von Willebrand's disease. *N Engl J Med* 2016;375:2067-80.
2. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood* 2015; 126:2038-46.
3. Tabor E. The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses and HIV type 1. *Transfusion* 1999;39:1160-8.
4. Berntorp E. Haemate P/Humate-P: a systematic review. *Thrombosis Res* 2009;124 Suppl 1:S11-4.
5. Budde U, Metzner HJ, Müller HG. Comparative analysis and classification of von Willebrand factor/factor VIII concentrates: impact on treatment of patients with von Willebrand disease. *Semin Thromb Hemost* 2006;32:626-35.
6. Lethagen S, Carlson M, Hillarp A. A comparative in vitro evaluation of six von Willebrand factor concentrates. *Haemophilia* 2004;10:243-9.
7. Kraaijenhagen RA, in't Anker PS, Koopman MM, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. *Thromb Haemost* 2000; 83: 5-9.
8. Dobrkovska A, Krzenski U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P in von Willebrand disease. *Haemophilia* 1998; 4 Suppl 3: 33-9.
9. Federici AB. The safety of plasma-derived von Willebrand/factor VIII concentrates in the management of inherited von Willebrand disease. *Expert Opin Drug Saf* 2009;8:203-10.
10. Gill JC, Ewenstein BM, Thompson AR, et al. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCO) to measure potency and to guide therapy. *Haemophilia* 2003;9:688-95.
11. Lillicrap D, Poon MC, Walker I, et al. Efficacy and safety of the factor VIII/von Willebrand factor concentrate, Haemate-P/Humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease. *Thromb Haemost* 2002;87:224-30.
12. Miesbach W, Krekeler S, Wolf Z, et al. Clinical use of Haemate(R) P in von Willebrand disease: a 25-year retrospective observational study. *Thromb Res* 2015;135:479-84.
13. Thompson AR, Gill JC, Ewenstein BM, et al. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P). *Haemophilia* 2004;10:42-51.
14. Makris M, Colvin B, Gupta V, et al. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand's disease. *Thromb Haemost* 2002;88:387-8.
15. Eikenboom JC. Congenital von Willebrand disease type 3: clinical manifestations, pathophysiology and molecular biology. *Best Pract Res Clin Haematol* 2001; 14: 365-79.
16. Federici AB, Mannucci PM. Management of inherited von Willebrand disease in 2007. *Ann Med* 2007; 39: 346-58.
17. Mannucci PM, Federici AB. Antibodies to von Willebrand factor in von Willebrand disease. *Adv Exp Med Biol* 1995; 386: 87-92.
18. Gunter KC, Luban NL. Transfusion-transmitted cytomegalovirus and Epstein-Barr virus diseases. In: Rossi EC, Simon TL, Moss GS, et al., editors. *Principles of transfusion medicine*. 2nd ed. Baltimore (MD): Lippincott Williams and Wilkins; 1996. pp. 717-32.
19. Abshire TC, Federici AB, Alvarez MT, et al. Prophylaxis in severe forms of von Willebrand's disease: results from the von Willebrand Disease Prophylaxis Network (VWD PN). *Haemophilia* 2013;19:76-81.
20. Auerswald G, Bade A, Haubold K, et al. No inhibitor development after continuous infusion of factor concentrates in subjects with bleeding disorders undergoing surgery: a prospective study. *Haemophilia* 2013;19:438-44.
21. Mannucci PM. Venous thromboembolism in von Willebrand disease. *Thromb Haemost* 2002;88:378-9.
22. Dangelo L, Platt CD, Broyles AD, et al. Case study of two consanguineous brothers with type 3 von Willebrand disease (VWD), inhibitors and anaphylactoid reaction to VWF [abstract OR022]. *J Thromb Haemost* 2015;13(Suppl 2):1-997.
23. Halimeh S, Krumpel A, Rott H, et al. Long-term secondary prophylaxis in children, adolescents and young adults with von Willebrand disease. Results of a cohort study. *Thromb Haemost* 2011; 105: 597-604.
24. Sanchez-Luceros A, Alberto ME, Kempfer AC, et al. Clinical and laboratory detection of transient neutralizing antibodies in severe von Willebrand disease on long term prophylaxis [abstract PO646-TUE]. *J Thromb Haemost* 2015;13(Suppl 2): 1-997.
25. Gröner A. Pathogen safety of plasma-derived products—Haemate P/Humate-P. *Haemophilia* 2008;14Suppl5:54-71.

26. Lethagen S, Kyrle PA, Castaman G, et al. von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost* 2007;5:1420-30.
27. Gill JC, Shapiro A, Valentino LA, et al. von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand disease. *Haemophilia* 2011;17:895-905.
28. Krause M, von Depka Prondzinski M, Halimeh S, et al. Haemate P for the treatment of vWD and haemophilia A: new results of a pharmacovigilance project [abstract PB 3.37-4]. *J Thromb Haemost* 2013;11(Suppl 2):290-1019.
29. Wermes C, Holzhauer S, Halimeh S, et al. Plasma-derived, purified, pasteurised von Willebrand factor/factor VIII concentrate in the treatment of patients with von Willebrand disease and haemophilia A: update of a long-term observational study [abstract PO647-MON]. *J Thromb Haemost* 2015;13(Suppl 2):1-997.
30. Knofler R, Siegert G, Stachele J, et al. Immune tolerance induction with Haemate P in hemophilia A: experience from a single center [abstract PO263-MON]. *J Thromb Haemost* 2015;13(Suppl 2):1-997.
31. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006; 29: 385-96.
32. Sharrar RG, Dieck GS. Monitoring product safety in the postmarketing environment. *Ther Adv Drug Saf* 2013; 4: 211-9.
33. Jacob D, Marrón B, Ehrlich J, et al. Pharmacovigilance as a tool for safety and monitoring: a review of general issues and the specific challenges with end-stage renal failure patients. *Drug Healthc Patient Saf* 2013;5:105-12.
34. Koster T, Blann AD, Briet E, et al. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995;345:152-5.
35. O'Donnell J, Laffan M. Elevated plasma factor VIII levels—a novel risk factor for venous thromboembolism. *Clin Lab* 2001;47:1-6.
36. Gill JC, Mannucci PM. Thromboembolic incidence with transiently elevated levels of coagulation factors in patients with von Willebrand disease treated with VWF:FVIII concentrate during surgery. *Haemophilia* 2014;20:e404-6.
37. Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med* 2016;374:2054-64.
38. Solomon C, Gröner A, Ye J, et al. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. *Thromb Haemost* 2015;113:759-71. 