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# Long-term efficacy and safety of a pasteurized, plasma-derived factor VIII concentrate (Beriate® P) in patients with haemophilia A

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ABSTRACT

*Introduction:* Beriate® P was first introduced in Germany in 1990 as factor VIII (FVIII):C® HS Behring and subsequent product improvements yielded an albumin-free formulation with a specific activity of approximately 170 IU/mg protein. In 1992, the concentration was raised to 100 IU FVIII/mL in the reconstituted product, with a mean specific activity of 270 IU/mg protein. Pathogen safety is achieved by careful donor selection and a combination of pasteurization and chromatographic purification steps.

*Materials and methods:* We analysed the efficacy and safety of Beriate® P in the clinical setting from 1996 to 2005 with a focus on surgical patients. Of the 36 patients (mean age: 38 years; range 1–72 years), 29 had severe haemophilia A, two had moderate haemophilia, two had mild haemophilia, and three had sub-clinical haemophilia. Most patients (n = 28) had more than 100 exposure days, representing a total of 202 patient-years with a consumption of 27,811,500 IU of Beriate® P.

*Results:* There was no evidence of seroconversion towards relevant viruses, no inhibitor development (35 previously treated patients, one previously untreated patient), no abnormal immunological findings or allergic reactions. In all 36 patients treated for acute bleeding and prophylaxis, and 24 surgeries (15 total joint replacements, eight orthopaedic procedures, one cholecystectomy) in 16 patients with severe haemophilia A, efficacy of Beriate® P was always rated as "excellent" or "good", and no thrombosis was reported.

*Conclusion:* Beriate® P has an excellent efficacy and safety profile. Many patients who were initiated on Beriate® P at our centre remain on the treatment today.



## Introduction

In 1990, a pasteurized clotting factor VIII (FVIII) concentrate was introduced in Germany under the brand name of FVIII:C® HS Behring. The original formulation contained albumin, which was later replaced by saccharose and glycine and registered in Germany as Beriate® P. This initial formulation had a FVIII concentration of 50 IU/mL and a specific activity of approximately 170 IU/mg protein. Subsequent advances in the production process enabled the solvent volume to be reduced and led to the launch in 1992 of Beriate® P with a FVIII concentration of 100 IU/mL and a mean specific activity of approximately 270 IU/mg protein. Other manufacturing developments have included a change in the diameter of the chromatography column to increase the FVIII yield, an improved purification process, and the optimization of the lyophilization programme for Beriate® P 500 and 1,000 IU FVIII.

Beriate® P is registered for the treatment and prophylaxis of hereditary haemophilia A and can be used in the treatment of acquired haemophilia A.

Fractionated plasma proteins such as Beriate® P are now considered to have an excellent safety profile; there have been no reports of virus transmissions in Germany caused by these products for more than 16 years [1]. A rigorous selection process for donors minimizes the potential risk for transmission of infectious diseases such as human immunodeficiency virus (HIV), causing acquired immunodeficiency syndrome (AIDS), or viral hepatitis, particularly the most common hepatitis A (HAV), hepatitis B (HBV) and hepatitis C (HCV) viruses. Furthermore, rigorous selection is also effective for other potential pathogens and diseases such as variant Creutzfeldt–Jakob disease (vCJD).

Virus inactivation procedures such as pasteurization further reduce the risk of virus transmission in that they effectively reduce/eliminate the potential virus load of a wide range of viruses (e.g. HIV, HBV, HCV, bovine diarrhoea virus), including newly identified pathogens (e.g. West Nile virus, severe acute respiratory syndrome, influenza A viruses [H1N1, H5N1]).

*Abbreviations:* AIDS, acquired immunodeficiency syndrome; CBR, complement binding reaction; CMV, cytomegalovirus; ED, exposure day; ELISA, enzyme-linked immunosorbent assay; FVIII, factor VIII; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MEIA, microparticle enzyme immunoassay; PCR, polymerase chain reaction; PTP, previously treated patients; PUP, previously untreated patient; vCJD, variant Creutzfeldt–Jakob disease.

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All single blood donations of source plasma (source plasma is plasma that is generated by plasmapheresis from selected donors) for production of Beriate® P are screened for anti-HIV type 1/2 antibodies, anti-hepatitis C antibodies, and hepatitis B surface antigen using serological assays. In addition, up to 512 donations are pooled into mini-pools and tested for relevant virus deoxyribonucleic acid or ribonucleic acid (RNA) (HCV, HBV, HAV, HIV, parvovirus B19) using polymerase chain reaction (PCR). In the event of a positive test result ("reactive" or above the defined threshold), the respective single donation is identified and discarded and the donor is (temporarily or permanently) excluded from further donation. Further testing (serological assays, genetic assays) takes place at the level of the manufacturing pool.

It has been estimated that up to 33% of haemophilia A patients develop FVIII neutralizing antibodies [2], and the occurrence of such antibodies/inhibitors is now considered to be one of the most serious complications in the treatment of haemophilia patients [3–5]. To determine the incidence of FVIII inhibitors and identify markers of virus transmission in our patient population receiving Beriate® P, we undertook a retrospective analysis of all patients who had received the treatment over a 10-year period.

## Materials and Methods

### *Study Design*

We identified all haemophilia A patients who had received treatment with Beriate® P (CSL Behring GmbH, Marburg, Germany) at our centre at any point between January 1996 and December 2005. All investigations relating to virus safety and other safety parameters were performed during the patients' 6-monthly or annual routine reviews. Substitution therapy and bleeding episodes were documented in patient diaries, with patients rating treatment efficacy as: "excellent"/"good", "sufficient", or "not sufficient" (requiring additional treatment). Analysis of the diaries was performed in a standardized manner every 3–6 months in our centre depending on the patient's clotting factor consumption. Patients were also questioned regarding treatment doses used, follow-up treatment required, and subjective overall treatment effectiveness ("excellent", "good", "sufficient", "not sufficient"). Patients who did not receive home therapy were treated at our centre and were documented there. In addition to the laboratory investigations undertaken, patients underwent a complete medical examination and their general and bleeding histories were recorded.

As we retrospectively analysed the data from our standard routine medical documentation, no ethical approval for this study was required. All patients provided informed consent for their data to be analysed for this study.

### *Virus Safety Assessments*

Virus safety was periodically determined by evaluating the virus status (determination of antibody titres against HAV and HBV [microparticle enzyme immunoassay, MEIA], HCV [MEIA and PCR], HIV [enzyme-linked immunosorbent assay, ELISA], Epstein–Barr virus [ELISA], herpes simplex virus [HSV; ELISA and complement binding reaction, CBR], cytomegalovirus [CMV; ELISA and CBR] and parvovirus B19 [Western blot]). All serological tests had to remain negative, with the exception of HSV and CMV, where titres below 1:40 were considered to be normal.

### *Immunoglobulin Assessments*

Immunoglobulins were assessed via nephelometry (immunoglobulin G, A and M, normal ranges: G: 700–1,600 mg/dL; A: 70–400 mg/dL; M: 40–230 mg/dL). In addition, lymphocyte differentiation, including CD4/CD8 ratio were evaluated.

### *Differentiation of Lymphocytes*

Differentiation of lymphocytes was investigated by determination of the total number of lymphocytes (normal range: 1,300–2,500/μL), total T3 lymphocytes (normal range: 980–1,900/μL), total B lymphocytes (normal range: 155–345/μL), T helper cells (CD4; normal range: 650–1,250/μl), T suppressor cells (CD8; normal range: 260–800/μL), ratio CD4/CD8 (normal range: 0.9–3.0), activated, total T cells (normal range: 59–228/μL), and total natural killer cells (normal range: 129–625/μL).

### *Replacement Therapy During Surgery*

In cases of surgery, we aimed for FVIII levels of around 100% at the time of surgery, followed by FVIII trough levels >70% until day 3 and >50% until the end of the first week. This required the use of 50–80 IU/kg body weight (b.w.) of clotting factor concentrate on the day of the operation, in line with treatment guidelines [6] to achieve FVIII levels of 100%, followed by the assessment of FVIII plasma level 30 minutes after administration. Depending on the timing of the surgery, another 1,000 IU was administered after 1 hour and, if the postoperative FVIII plasma level after 6 hours was below 60%, another 30 IU/kg b.w. was administered. On the first and second (and sometimes third) postoperative day, approximately 2,000 IU, calculated according to patient body weight, was administered every 8 hours and plasma FVIII level was checked daily. Patients also received oral tranexamic acid; we did not administer heparin for thromboprophylaxis.

## Results

### *Patient Demographics*

Over the 10-year period evaluated, 36 patients (mean age: 38 years; range: 1–72 years; one patient was 1 year old, one was 13 years old, and the remainder were adults) with haemophilia A had received Beriate® P as on-demand treatment (19 patients), for surgery (16 patients) or prophylaxis, including intermittent secondary prophylaxis (17 patients) before and after surgery or excessive bleeding. Overall, 29 patients had severe haemophilia A, two had moderate haemophilia, two had mild haemophilia, and three had sub-clinical haemophilia. One patient was previously untreated (PUP); the remaining 35 patients were previously treated (PTPs) with cryoprecipitate (owing to the treatment practice in the former eastern part of Germany at that time), with most (n = 28) having more than 100 exposure days (EDs) – representing 202 patient-years (mean 5.6 years/patient) and a consumption of 27,811,500 IU of Beriate® P. In total, nine patients received treatment for the entire 10-year study period. There were no HIV-positive individuals in the sample; 12 patients were PCR-positive for HCV as a result of prior use of cryoprecipitate. Demographic data and mutation type are summarized in Table 1.

Of the patients identified in the original sample, 25 are still using Beriate® P for replacement therapy; the remaining patients have either died (3/36 patients) or switched to recombinant FVIII products (8/36 patients).

### *Beriate® P Consumption*

The consumption of Beriate® P varied significantly between patients (Table 2), ranging from 2,000 IU over 1 year of treatment (patient 4 with mild haemophilia A) to almost 2,900,000 IU over 10 years of treatment (patient 24 with severe haemophilia A who underwent two surgical procedures). Within the total patient group, the consumption of Beriate® P over the 10 years assessed was 27,811,500 IU. Analysed per year and per patient, a mean consumption of 138,362 IU was seen in patients with severe haemophilia A (Table 2). The average doses per

patient, per year, per kg (all patients and severe patients only) were 1,416 IU and 1,739 IU, respectively.

### *Efficacy of Beriate® P*

Sixteen haemophilia A patients underwent 24 surgical procedures, including 15 total joint replacements, eight orthopaedic procedures and one cholecystectomy (Table 3). A total of 1,856,000 IU of Beriate® P was administered and of those, 1,095,000 IU was administered during total knee replacement surgery (in one case, a total hip replacement was also performed). The mean consumption (± standard deviation) per operation per patient was 949 ± 345 IU/kg. The median consumption per operation per patient was 892 IU/kg.

During home treatment of bleeds, there were no failures of efficacy. Beriate® P was rated as "excellent" or "good" by all patients. Nearly 80% of bleeding events responded to the first administration of Beriate® P in almost 4,000 bleeds in all patients; the remaining 20% of bleeds required two or more administrations.

### *Safety of Beriate® P*

Throughout the entire 10-year observation period, there were no seroconversions for the virus parameters investigated, including HIV, HAV, HBV and HCV. There were no adverse events (including allergic reactions) recorded during the administration of Beriate® P in our study. There were no reports of thrombosis, and no inhibitors were identified in any of our patients. At the time of this study, one patient with severe haemophilia A had experienced less than 10 EDs. We did not find any significant abnormalities in the immunological parameters investigated, including the CD4/CD8 ratio.

**Table 1**
Patient demographics and genetic mutations.

| Patient number | Year of birth | Age (years) | Weight (kg) | Severity of haemophilia A | FVIII (%) | Genetic mutation |
|---|---|---|---|---|---|---|
| 1 | 1959 | 46 | 79 | Severe | <1 | Missense mutation Val(GTT) 708Phe(TTT) |
| 2 | 1985 | 20 | 93 | Severe | <1 | Intron-22 inversion |
| 3 | 1985 | 20 | 70 | Severe | <1 | Intron-22 inversion |
| 4 | 1966 | 39 | 84 | Mild | 10 | NA |
| 5 | 1966 | 39 | 70 | Severe | <1 | NA |
| 6 | 1981 | 24 | 63 | Severe | <1 | Small deletion c.4372-4379delA |
| 7 | 1933 | 72 | 73 | Severe | <1 | NA |
| 8 | 1961 | 44 | 101 | Severe | <1 | Insertion (c.1137-1138insT) |
| 9 | 1968 | 37 | 73 | Severe | <1 | Huge deletion of exons 2–6 |
| 10 | 1959 | 46 | 78 | Severe | <1 | Missense mutation Glu(GAG) 110 Asp (GAC) |
| 11 | 1960 | 45 | 73 | Severe | <1 | Missense mutation Glu(GAG) 110 Asp (GAC) |
| 12 | 1955 | 50 | 103 | Severe | <1 | Intron-22 inversion |
| 13 | 1953 | 52 | 75 | Mild | 6 | NA |
| 14 | 1968 | 37 | 135 | Sub-clinical haemophilia | 32 | Missense mutation His(CAT)632 Leu (CTT) |
| 15 | 1981 | 24 | 82 | Severe | <1 | NA |
| 16 | 1984 | 21 | 73 | Severe | <1 | Intron-22 inversion |
| 17 | 1966 | 39 | 89 | Moderate | 4 | NA |
| 18 | 1965 | 42 | 96 | Moderate | 4 | NA |
| 19 | 1983 | 22 | 76 | Severe | <1 | Huge deletion in exon 6 |
| 20 | 1972 | 33 | 69 | Severe | <1 | Deletion (3629-363delA) |
| 21 | 1952 | 53 | 75 | Severe | <1 | Intergene and intragene RFLP |
| 22 | 1947 | 58 | 95 | Severe | <1 | Intron-22 inversion |
| 23 | 1992 | 13 | 71 | Severe | <1 | Intron-22 inversion |
| 24 | 1953 | 52 | 100 | Severe | <1 | Intron-22 inversion |
| 25 | 1965 | 40 | 85 | Severe | <1 | Intron-22 inversion |
| 26 | 1965 | 40 | 84 | Severe | <1 | Intron-22 inversion |
| 27 | 1982 | 23 | 68 | Severe | <1 | NA |
| 28 | 1966 | 39 | 74 | Severe | <1 | Missense mutation Ile(ATC) 76Thr(ACC) |
| 29 | 1955 | 50 | 90 | Severe | <1 | NA |
| 30 | 1976 | 29 | 80 | Severe | <1 | Missense mutation Arg(CGT) 1781His(CAT) |
| 31 | 1959 | 46 | 68 | Sub-clinical haemophilia | 15 | NA |
| 32 | 1981 | 24 | 91 | Severe | <1 | Intron-22 inversion |
| 33 | 1955 | 50 | 82 | Sub-clinical haemophilia | 32 | NA |
| 34 | 2005 | 1 | 10 | Severe | <1 | Intron-22 inversion |
| 35 | 1957 | 48 | 80 | Severe | <1 | Intron-22 inversion |
| 36 | 1961 | 44 | 78 | Severe | <1 | NA |

NA, not available; RFLP, restriction fragment length polymorphism.

**Table 2**
Days of exposure, years of therapy, and Beriate® P consumption.

| Patient number (haemophilia severity) | Days of exposure | Years of therapy | Total factor VIII consumption (IU) | Consumption/year (average IU) | Consumption/year/kg (IU/kg body weight) |
|---|---|---|---|---|---|
| 1 (severe) | >100 | 5 | 596,000 | 119,200 | 1,509 |
| 2 (severe) | >100 | 3 | 456,000 | 152,000 | 1,634 |
| 3 (severe) | >100 | 5 | 600,000 | 120,000 | 1,714 |
| 4 (mild) | <50 | 3 | 6,000 | 2,000 | 24 |
| 5 (severe) | >100 | 10 | 1,202,000 | 120,200 | 1,717 |
| 6 (severe) | >100 | 10 | 1,605,000 | 160,500 | 2,548 |
| 7 (severe) | >100 | 3 | 364,000 | 121,000 | 1,658 |
| 8 (severe) | >100 | 3 | 166,000 | 55,300 | 548 |
| 9 (severe) | >100 | 3 | 513,000 | 171,000 | 2,342 |
| 10 (severe) | >100 | 10 | 689,000 | 68,900 | 883 |
| 11 (severe) | >100 | 10 | 310,000 | 31,000 | 425 |
| 12 (severe) | >100 | 9 | 1,176,000 | 130,600 | 1,268 |
| 13 (mild) | <50 | 2 | 14,000 | 7,000 | 93 |
| 14 (sub-clinical) | 10 | 1 | 14,000 | 14,000 | 104 |
| 15 (severe) | >100 | 5 | 152,000 | 30,400 | 371 |
| 16 (severe) | >100 | 4 | 600,000 | 150,000 | 2,055 |
| 17 (moderate) | <50 | 1 | 6,000 | 6,000 | 67 |
| 18 (moderate) | <50 | 1 | 4,000 | 4,000 | 42 |
| 19 (severe) | >100 | 5 | 650,000 | 130,000 | 1,711 |
| 20 (severe) | >100 | 10 | 1,740,000 | 174,000 | 2,522 |
| 21 (severe) | >100 | 6 | 632,000 | 105,300 | 1,404 |
| 22 (severe) | >100 | 7 | 2,510,000 | 358,600 | 3,775 |
| 23 (severe) | >100 | 10 | 1,140,000 | 114,000 | 1,606 |
| 24 (severe) | >100 | 10 | 2,869,000 | 286,900 | 2,869 |
| 25 (severe) | >100 | 10 | 1,150,000 | 115,000 | 1,353 |
| 26 (severe) | >100 | 3 | 642,000 | 214,000 | 2,548 |
| 27 (severe) | >100 | 9 | 1,361,000 | 151,200 | 2,224 |
| 28 (severe) | >100 | 5 | 1,283,000 | 213,800 | 2,889 |
| 29 (severe) | >100 | 2 | 240,000 | 120,000 | 1,333 |
| 30 (severe) | >100 | 8 | 371,000 | 46,300 | 597 |
| 31 (sub-clinical) | 14 | 1 | 12,000 | 12,000 | 176 |
| 32 (severe) | >100 | 10 | 2,163,000 | 216,300 | 2,377 |
| 33 (sub-clinical) | 4 | 2 | 5,000 | 2,500 | 30 |
| 34 (severe) | 7 | 1 | 3,500 | 3,500 | 350 |
| 35 (severe) | >100 | 9 | 1,697,000 | 188,500 | 2,356 |
| 36 (severe) | >100 | 6 | 870,000 | 145,000 | 1,859 |
| Total | | 202 | 27,811,500 | 112,778 (mean all patients) 138,362 (mean severe patients) | 1,416 (mean all patients) 1,739 (mean severe patients) |

**Table 3**
Surgical procedures conducted under Beriate® P.

| Patient number | Type of surgery | Days in hospital (n) | Consumption (IU) | Consumption (IU/kg body weight) |
|---|---|---|---|---|
| 1 | Synovectomy ankle | 10 | 36,000 | 456 |
| 2 | Cholecystectomy | 5 | 35,000 | 376 |
| 5 | Total knee replacement | 19 | 86,000 | 1,229 |
| 5 | Arthrodesis ankle | 13 | 64,000 | 914 |
| 7 | Arthrodesis knee | 22 | 104,000 | 1,425 |
| 8 | Total knee replacement | 20 | 92,000 | 911 |
| 10 | Total knee replacement | 22 | 95,000 | 1,218 |
| 10 | Total knee replacement | 13 | 63,000 | 808 |
| 12 | Total knee replacement | 15 | 90,000 | 874 |
| 12 | Total knee replacement | 14 | 82,000 | 796 |
| 19 | Pseudotumour small pelvis | 8 | 25,000 | 329 |
| 20 | Total knee replacement | 22 | 95,000 | 1,377 |
| 20 | Total hip replacement | 13 | 53,000 | 768 |
| 21 | Total knee and hip replacement | 24 | 85,000 | 1,133 |
| 21 | Total hip replacement | 19 | 65,000 | 867 |
| 24 | Correction of valgus | 20 | 114,000 | 1,140 |
| 24 | Pseudotumour small pelvis | 11 | 70,000 | 700 |
| 28 | Total knee replacement | 14 | 59,000 | 797 |
| 29 | Total knee replacement | 19 | 118,000 | 1,311 |
| 30 | Cyst surgery talus and synovectomy ankle | 9 | 45,000 | 563 |
| 35 | Total knee replacement | 17 | 108,000 | 1,350 |
| 35 | Total hip replacement | 23 | 98,000 | 1,225 |
| 35 | Synovectomy elbow | 12 | 52,000 | 650 |
| 36 | Total knee replacement | 22 | 122,000 | 1,564 |
| Total | | | 1,856,000 | 22,781 |

## Discussion

Our results support previous observations that virus-inactivated, human plasma-derived coagulation factor concentrates have an excellent safety profile [7–12]. Although only 36 patients received Beriate® P during the 10-years of observation in this study, over 27 million IUs of the product were administered without transmission of viruses or the development of inhibitors in PTPs or the PUP.

Kreuz and colleagues have previously published the results of a virus safety study of pasteurized clotting factor concentrates [7,10] and reported no transmission of HAV, HBV or HCV [7], and no cases of seroconversion to HIV-1 or HIV-2 [10]. In contrast, of 99 patients with haemophilia A or von Willebrand disease who had been treated with human-plasma-derived clotting products not including specific steps to inactivate or remove viruses, a positive reaction for HIV-1 or HIV-2 antibodies was detected in 59 patients [7,10].

In a longitudinal study of 113 patients with haemophilia A or B, von Willebrand disease, or factor X deficiency receiving only pasteurized concentrates, again, no seroconversion for HIV was observed over a follow-up period of up to 11 years [13].

Another landmark study has demonstrated the safety of a pasteurized FVIII concentrate with regard to hepatitis in patients with haemophilia and no previous infusions [9]. Data from other study groups [11,12] have confirmed the safety of virus-inactivated plasma-derived coagulation factor concentrates.

To minimize the risk of viral transmission, human plasma-derived clotting products undergo several production steps that effectively reduce prion load [14–16] by >10 $\log_{10}$ [17]. This increased safety also keeps the theoretical risk of transmitting prions and their associated diseases such as vCJD as small as possible. Only one suspected case of vCJD transmission has been reported in a haemophilia patient who was without any clinical signs of vCJD and whose treatment included one batch of FVIII product that was manufactured from plasma of a donor who developed symptoms of vCJD 6 months after donating the plasma in the UK in 1996 [18]. Results from the "US Food and Drug Administration plasma-derived FVIII risk assessment model" suggest that the risk of the potential of plasma-derived FVIII products to transmit vCJD infection "is highly uncertain, but appears likely to be extremely small" [19].

Turning now to inhibitor risk in haemophilia patients, a publication by Roussel-Robert et al. in 2003 described a prevalence of inhibitors in severe PTPs of 6.1% for a B-domain-deleted recombinant product [20]. In contrast, Lusher et al. reported just one FVIII inhibitor in 113 PTPs using the same B-domain-deleted recombinant product [21]. In a follow-up study [22], the inhibitor rate in PTPs remained unchanged, as did the inhibitor rate in PUPs (32 inhibitors in 101 PUPs; 32%).

Yoshioka et al. reported an incidence of high-titre FVIII inhibitors of 11.6% in PUPs receiving a recombinant, baby hamster kidney cell-derived FVIII preparation [23], while Kreuz et al. reported an incidence of 15% in 37 PUPs and 24 minimally treated patients receiving the full-length sucrose-formulated version of this recombinant FVIII [24]. Other studies have reported low inhibitor frequencies in PTPs (one patient of 108 PTPs investigated) for a recombinant FVIII product prepared using a plasma/albumin-free method [25]; PUP data for this product were reported to be in the region of 28% [26]. Inhibitor incidence in PUPs for the predecessor of this product was 31% [27].

Inhibitor generation has also been observed with different plasma-derived FVIII products, where the incidence of inhibitors was found to be up to 52% in patients with severe haemophilia A and who received crude and intermediate-purity concentrates [2]. Comparing inhibitor data for patients with severe haemophilia A receiving recombinant FVIII products were limited (only two of 46 patients treated), and in a follow-up of this study over a 23-year period, differences in immunogenicity between plasma-derived and recombinant FVIII products could not be confirmed [8]. In that follow-up study, the number of patients presenting with over 200 EDs was 64% for those receiving plasma-derived products compared with 35% for those receiving recombinant products [8]. Interestingly, a review by Wight and Paisley revealed that the incidence of inhibitors was lower in haemophilia A patients using a single plasma-derived FVIII product than in those using a single recombinant FVIII product [28].

The question of whether inhibitor risk is best investigated in PTPs or PUPs is controversial. In the late 1990s, an International Society on Thrombosis and Haemostasis (ISTH) subcommittee proposed that PTPs with more than 150 exposure days formed the appropriate study population for this purpose [29]. However, higher inhibitor rates seem to occur in PUPs, which may suggest a greater sensitivity for earlier detection of inhibitory potential in this population [30].

Several risk factors for inhibitor generation have been identified that are unrelated to the type of product used: a high-risk FVIII gene defect, a positive family history of inhibitors, ethnicity, polymorphisms in the immune-regulating genes, age at first exposure to FVIII, and intensive treatment [31]. Based on results obtained from the CANAL study [32], the odds ratios (univariate analyses) for the different factors were 4.0 (positive family history of inhibitors), 3.3 (high risk gene mutation type), 6.8 (intensive treatment, 5 days, at first treatment), 2.8 (age at first exposure <1 month), and 7.4 (surgery as reason for first treatment) [30]. As these risk factors have not been taken into account during most inhibitor studies, potential study bias cannot be excluded.

In summary, over a period of 10 years of use, Beriate® P was shown to have an excellent efficacy and safety profile. The product did not induce inhibitors and was not associated with thrombosis during or after surgery. Beriate® P became available in Germany in 1990 and, thanks to its excellent efficacy and safety profile, is still being used today.

## Conflict of Interest Statement

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