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Clinical assessment of Optivate®, a high-purity concentrate of factor VIII with von Willebrand factor, in the management of patients with haemophilia A

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Summary. Factor VIII (FVIII) concentrates have revolutionized the treatment of patients with haemophilia A. Concerns over the transmission of viral infections through these products have been addressed through stringent, donor-screening procedures and robust antiviral manufacturing steps. Bio Products Laboratory has developed a high-purity FVIII product with von Willebrand factor, Optivate®. Its safety, tolerability and efficacy as prophylaxis and treatment of bleeds have been established in long-term studies. Seventy previously treated patients with severe haemophilia A, with ≥20 exposure days, were recruited into two long-term, multicentre, open-label studies. The protocols were virtually identical. Patients received Optivate® either prophylactically or on-demand. A mean of 159.0 EDs were experienced over 11 320 infusions. Under both conditions, Optivate® was well tolerated. Only 10% of patients experienced a treatment-related adverse event; the most commonly reported were headache (4% of patients) and dizziness (3% of patients). The mean number of bleeds/patient over the 2 year treatment period was 23.5 during prophylactic use and 70.4 during on-demand use. In patients treated prophylactically, clinical responses to breakthrough bleeds were rated by physicians as excellent or good and as very helpful or helpful by patients in 95% of bleeds. Clinical responses for on-demand patients were rated as excellent or good by physicians and helpful or very helpful by the patients for 91% of bleeds. There were no viral transmissions or inhibitors. The studies confirm the clinical efficacy and safety of Optivate® in both prophylactic and on-demand management of patients with haemophilia A.

Keywords: efficacy, factor VIII, haemophilia A, plasma-derived concentrates, safety

Introduction

It is well known that factor VIII (FVIII) concentrates have revolutionized the treatment of patients with haemophilia, with considerable improvements in patients' quality of life [1,2]. The transmissions of hepatitis A (HAV), hepatitis B (HBV), non-A–non-B hepatitis [3,4] and HIV [5,6] were significant setbacks. Many preventive measures were implemented to reduce the risk of viral transmission by transfusion and plasma products, including donor screening, virucidal procedures [5–9] and virus eradication steps in manufacturing. For example, in 1985, Bio Products Laboratory (BPL) introduced an intermediate-purity FVIII/von Willebrand factor (VWF) concentrate (8Y) manufactured using a dry heat-treatment at 80°C for 72 h [10–12], which is known to have broad antiviral effect [10,13]. Over the last 20 years, 8Y has been well

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tolerated in the treatment of haemophilia A and von Willebrand disease (VWD), without any transmission of hepatitis A, hepatitis B or hepatitis C or HIV, and with a low incidence of inhibitors [14–16].

A new high-purity product, Optivate® (Bio Product Laboratory, Elstree, UK), has been developed, which includes a novel chromatographic purification step to remove unnecessary proteins, such as fibrinogen and fibronectin. In addition, the specific and well-established solvent–detergent step is included, to minimize transmission of enveloped viruses, including West Nile [17,18]. The dry heating (80°C for 72 h) process, used in 8Y, and known to inactivate SARS virus [19], has been retained. The two specific virucidal steps taken in the manufacture of Optivate® are considered effective against enveloped and non-enveloped viruses (e.g. HAV and parvovirus B19). The normal pharmacokinetics of Optivate® have been reported elsewhere in patients with haemophilia A [20] and in patients with VWD [21].

Nowadays, the development of inhibitor antibodies remains a concern with new FVIII products. In the late 1980s and early 1990s, two outbreaks of inhibitors amongst previously treated patients (PTPs) treated with new concentrates showed that changes in manufacturing processes could result in the formation of neoantigens leading to inhibitor formation [22–25]. Since then, it has been essential to evaluate all new FVIII concentrates in PTPs to establish whether they are unusually antigenic.

This paper reports consolidated clinical data, collected prospectively, over a follow-up period of 2 years, from two studies conducted to assess the safety and efficacy of Optivate® in patients with severe haemophilia A.

Materials and methods

Study design

Two studies [called pharmacokinetic (PK) and safety and efficacy (SE)] were conducted; as their designs were virtually identical, the long-term clinical data have been combined in this report. The major difference between the studies was that one of them (PK) additionally provided pharmacokinetic profiles of the patients' previous FVIII and of Optivate®. These PK data are reported elsewhere [20]. Both studies were multicentre, international, open-label, non-randomized, prospective studies compliant with the guidelines issued by the Committee for Proprietary Medicinal Products (CPMP), now known as the Committee for Medicinal Product for Human use (CHMP) [26]. Ethics committee approval and written informed consent were obtained.

Clinical assessments and the visit schedules were identical in both studies: a prestudy screening (2 weeks prior to Optivate® being given); a first-dose assessment, followed by 3 months of home therapy; a second-dose assessment at the end of this period, followed by a further 21 months of home therapy; with regular follow-up over the phone throughout and 3-monthly reviews at the haemophilia centre.

Patients

Patients were eligible for inclusion if they were male, ≥12 years old, had haemophilia A (<2% basal FVIII activity at the time of diagnosis) without inhibitors, with at least 20 exposure days (ED; but >150 for SE study). Exclusion criteria were history of inhibitors; international normalized ratio >1.5; thrombocytopenia (platelets $<50 \times 10^9$ L^{-1}), clinically significant renal disease (creatinine >200 μmol L^{-1}); clinically significant liver disease (alanine transaminase levels > three times the upper normal limit); participation in another clinical trial within 30 days before study entry. In the SE, study patients needed to have CD4 lymphocyte counts of $>0.4 \times 10^9$ L^{-1}. Patients were recruited at Haemophilia centres in Poland and the UK.

Treatments

Optivate® was used prophylactically or on-demand, according to preference. No specific medications were prohibited during the study, with the exception of other FVIII products.

Outcome variables

Safety was assessed by monitoring viral markers (anti-parvovirus B19, HIV, HBV, HCV, and HAV) at specified times, FVIII inhibitor screens (3 monthly), routine biochemistry and haematology, and adverse events (AEs). FVIII inhibitor screens were performed using standard activated partial thromboplastin time incubation techniques, as recommended by UK Haemophilia Centre Doctors' Organization (UKHCDO) [26–28]. If a screening test was positive, a Bethesda/Nijmegen quantitation assay was performed.

The extent of exposure was also determined. Efficacy was assessed by the number, type and severity of bleeds as a new bleed (break-through bleed) or ongoing bleed, (bleed requiring additional Optivate® doses). Subjective assessments of haemostasis were made by the clinician and the patients.

Statistical methods

The sample sizes chosen for each study were in excess of that prescribed in the CHMP guidance [26]. Descriptive statistics are presented and subdivided into prophylactic and on-demand use. As these modalities of treatment

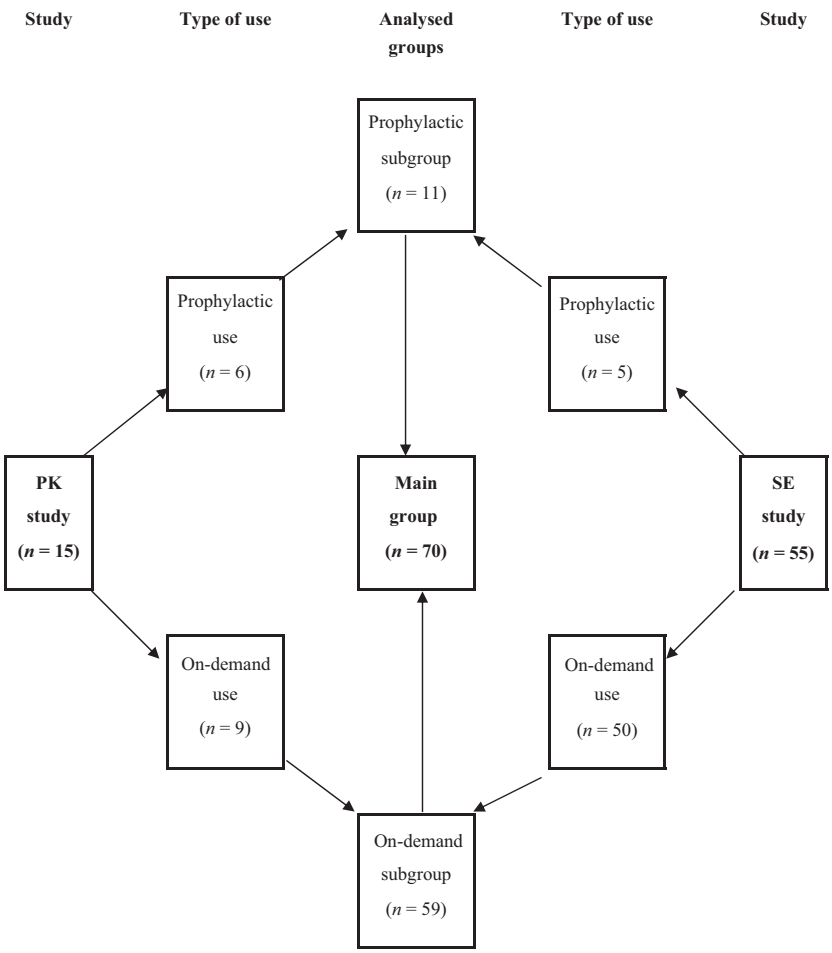

Fig. 1. Flow of participants in the studies to the analysed groups.

were not randomized, no formal, comparative, statistical tests were used. Prophylaxis was defined as at least two prophylactic doses per week.

Results

Patients studied

A total of 70 patients were enrolled (15 in the PK study; 55 in the SE study). All, except one African-Caribbean patient, were Caucasian. Of the 70 patients, 11 were treated prophylactically and 59 on-demand (Fig. 1).

Table 1. Consolidated patient demographics.

Variable/stats	Prophylactic use *n* = 11	On-demand use *n* = 59	Overall *n* = 70
Age (years)			
Mean	33.5	30.5	30.9
Range	20–48	12–65	12–65
Weight (kg)			
Mean	78.5	70.8	72.0
Range	55–100	32–106	32–106
Duration of prior factor VIII treatment (years)			
Mean	21.6	13.9	14.8
Range	8–37	3–50	3–50

Of the 59 on-demand patients, 47 administered intermittent prophylactic doses, mostly before increased physical activity. Consolidated baseline demographics of the participants are shown in Table 1.

Efficacy

Duration and infusions. Patients received Optivate® for a mean period of 92.9 weeks (Table 2).

There was no significant difference in the mean duration of treatment per patient between the two Optivate® usage groups (97.2 weeks in the prophylactic group and 92.1 weeks in the on-demand group). Overall experience in the study was 124.6 patient-years. Altogether 11 320 infusions of Optivate® were used.

Table 2. Duration of Optivate® therapy.

	Prophylactic group	On-demand group	Overall
Mean duration in weeks (Min, Max)	97.3 (93.1, 104.7)	92.1 (10.1, 109.9)	92.9 (10.1, 109.9)
Patient-years	20.5	104.1	124.6

Min, minimum; Max, maximum.

Table 3. Exposure days to Optivate® for prophylactic and on-demand subgroups.

Stats	Prophylactic sub-group (n = 11)	On-demand sub-group (n = 59)	Overall (n = 70)
To treat a bleed			
Mean (95% CI)	33.9 (10.24;57.58)	93.7 (78.77;108.58)	84.3 (70.36;98.21)
Prophylactically			
Mean (95% CI)	253.4 (221.18;285.55)	37.3 (23.38;51.16)	71.2 (48.62;93.84)
Overall**			
Mean (95% CI)	289.6 (243.12;336.15)	134.7 (117.70;151.62)	159.0 (138.39;179.64)

CI, confidence interval.
*An exposure day = a day when the patient received at least one infusion, whether it was administered as prophylaxis or on-demand for a bleed.
**Including bolus doses at recovery assessments.

The study recorded a mean of 159.0 EDs (Table 3), which included in the patients on prophylaxis 2789 doses prophylactically and 408 infusions to treat a bleed and those on-demand using 5580 infusions to treat a bleed and 2205 doses for intermittent prophylaxis (Table 4).

Overall, the mean number of infusions administered per patient was 161.7. The Polish subjects had fewer EDs per patient than the UK patients (Table 5).

Doses of Optivate®. When a bleed occurred in patients on prophylaxis, the mean dose/patient used for a new bleed was 25.0 IU kg^{-1} and the mean total for an ongoing bleed was 53.6 IU kg^{-1} per patient. In comparison, the on-demand patients used slightly lower doses for new and ongoing bleeds (Table 6).

In addition to the 11 patients in the prophylactic group, 47 on-demand patients were administered intermittent prophylactic doses. Overall, the mean prophylactic dose was 13.7 IU kg^{-1} per patient: 17.6 IU kg^{-1} in the prophylactic group and 13.0 IU kg^{-1} for intermittent prophylaxis in the on-demand group (Table 7). Patients in the UK used a higher prophylactic dose per infusion than those in Poland and administered more frequent prophylactic doses; 1.63 and 0.54 prophylactic doses per week per patient, respectively (Table 8).

Treatment of spontaneous bleeds during the study. The mean number of bleeds per patient was 23.5 for patients using Optivate® prophylactically (mean 0.24 new bleeds per week per patient) compared to 70.4 for on-demand patients (mean 0.75 new bleeds per week per patient). The UK patients had a mean bleed rate of 0.49 bleeds per week per patient, whereas the Polish patients had 0.72 bleed per week per patient (Table 9).

Overall, 78% of the bleeds were into the joints, 11% were muscle bleeds and 9% were open/other bleeds and for the remaining 1%, location was not specified (Table 6).

The objective outcome of the bleeding episodes was assessed by the clinicians for 84.2% of bleeds and in 97.4% of bleeds by patients. For patients treated prophylactically, the clinicians rated Optivate® therapy as excellent or good in 95% of the assessed bleeding episodes. The patients reported clinical responses of helpful or very helpful in controlling bleeding episodes in 95% of assessed bleeds in the prophylactic group and in 91% of those in the on-demand group (Table 10).

Safety

Consolidated AEs. In the prophylactic group, one patient (9%) reported five treatment-related AEs. In

Table 5. Exposure** days for all subjects – UK vs. Poland.

	n	No. of exposure days	Mean	95% LCL	95% UCL
Exposure** days per subject for UK	13	2727	209.8	138.84	280.70
Exposure** days per subject for Poland	57	8402	147.4	127.70	167.17

LCL, lower confidence interval; UCL, upper confidence interval.
**Including bolus doses at recovery assessment.

Table 4. Overall number of Optivate® infusions for prophylactic and on-demand subgroups.

Number of infusions	Prophylactic sub-group (n = 11)	On-demand sub-group (n = 59)	Overall (n = 70)
To treat a bleed			
Total	408	5580	5988
Mean (95% CI)	37.1 (10.13;64.05)	94.6 (79.45;109.70)	85.5 (71.42;99.67)
Prophylactically			
Total	2789	2205	4994
Mean (95% CI)	253.6 (221.29;285.80)	37.4 (23.35;51.39)	71.3 (48.67;94.02)
Overall**			
Mean (95% CI)	295.8 (247.45;344.18)	136.7 (119.38;154.04)	161.7 (140.56;182.87)

CI, confidence interval.
**Including bolus doses at recovery assessment.

Table 6. Duration of bleeds and doses of Optivate® needed to control bleeding episodes.

	Prophylactic group (n = 11)	On-demand group (n = 59)	Overall (n = 70)
All bleeds			
Total no. bleeds	258	4151	4409
Mean/patient	23.5	70.4	63.0
Mean duration/patient (h)†	9.5 (CI: 4.90;14.12)	13.7 (CI: 10.72;16.73)	13.1 (CI: 10.43;15.66)
Median duration/patient (h)†	9.00	10.81	10.13
Mean dose per infusion/patient IU/kg	41.5 (CI: 14.44;68.46)	26.0 (CI: 22.15; 29.90)	28.5 (CI: 23.38;33.52)
Bleeds/week/patient	0.24 (CI: 0.08;0.40)	0.75 (CI: 0.65;0.86)	0.67 (CI: 0.57;0.78)
New bleeds			
Mean dose/patient IU/kg	25.0 (CI: 15.67;34.35)	18.2 (CI: 16.66;19.78)	19.3 (CI: 17.37;21.20)
Ongoing bleeds			
Mean dose/patient IU/kg	53.6 (CI: −8.11; 115.36)	26.4 (CI: 21.15; 31.55)	29.9 (CI: 21.71;38.15)
Joint bleeds‡			
Total no. bleeds	‡220	‡3233	‡3453
Mean dose/patient IU/kg	30.4 (CI: 21.22;39.49)	26.0 (CI:22.17;29.74)	26.6 (CI: 23.16;30.02)
Muscle bleeds‡			
Total no. bleeds	‡16	‡470	‡486
Mean dose/patient IU/kg	30.9 (CI: 16.81;44.94)	25.6 (CI: 21.13;30.09)	26.2 (CI: 22.11;30.38)
Open/other‡			
Total no. bleeds	‡21	‡386	‡407
Mean dose/patient IU/kg	52.6 (CI: −20.90;126.18)	30.8 (CI: 22.74; 38.78)	32.8 (CI: 24.10;41.47)

CI, confidence interval.
†Dataset not normally distributed.
‡For 63 bleeds, location was not specified.

the on-demand group, 6 patients (10%) reported an AE (17 events). Overall, 22 treatment-related AEs occurred in seven patients (10%). Headache was the most frequent AE, which occurred for three (4%) patients, then dizziness, reported by two (3%) patients (Table 11). Overall, one AE occurred for every 894 infusions.

Table 7. Prophylactic use of Optivate®.

	Prophylactic group	On-demand group
Total number of infusions	2789	2205
Mean dose per subject IU/kg	17.6	13.0
95% CI	13.05;22.13	10.64;15.38
Mean number of doses	253.6	37.37
Range	197–343	0–197
95% CI	221.29; 285.80	23.35;51.39
Mean number of doses per week per subject	2.6	0.4
Range	2.06–3.66	0–1.96

CI, confidence interval.

Table 8. Prophylactic doses summary for all subjects – UK vs. Poland.

	n	No. of infusions	Mean	95% LCL	95% UCL
No. of infusions per week per subject for UK	13	2018	1.63	0.79	2.46
Dose (IU/kg) per infusion for UK			18.6	18.31	18.98
No. of infusions per week per subject for Poland	57	2976	0.54	0.35	0.73
Dose (IU/kg) per infusion for Poland			14.4	14.13	14.59

LCL, lower confidence interval; UCL, upper confidence interval.

Other safety variables. All patients had negative screens for inhibitors to FVIII throughout the studies; no virus transmissions occurred, and there were no significant changes in laboratory values.

Table 9. Treatment of all bleeds for UK vs. Poland.

	n	No. of bleeds	Mean	95% LCL	95% UCL
No. of bleeds per week per subject for UK	13	593	0.49	0.23	0.76
Dose per bleed (IU/kg) for UK			24.9	23.68	26.05
No. of bleeds per week per subject for Poland	57	3816	0.72	0.60	0.83
Dose per bleed (IU/kg) for Poland			24.8	23.99	25.51

LCL, lower confidence interval; UCL, upper confidence interval.

Table 10. Response rates assessed by clinicians and patients for bleeding episodes in patients managed with Optivate® given prophylactically or on-demand.

	Prophylactic	On-demand
Clinicians' assessment		
Excellent	39 (53%)	1151 (32%)
Good	31 (42%)	2134 (59%)
Moderate	3 (4%)	336 (9%)
None	0 (0%)	17 (0%)
Not available	185	513
Patients' assessment		
Very helpful	124 (50%)	1272 (31%)
Helpful	110 (45%)	2418 (60%)
Helped a little	10 (4%)	327 (8%)
Did not help	2 (1%)	30 (1%)
Not available	12	104

Table 11. Summary of treatment-related AEs.

	Number (%) of patients					
	Prophylactic use (*n* = 11)		Spontaneous use (*n* = 59)		Overall (*n* = 70)	
	No. (%) of patients reporting AEs	No. of events	No. (%) of patients reporting AEs	No. of events	No. (%) of patients reporting AEs	No. of events
Total no.	1 (9%)	5	6 (10%)	17	**7 (10%)**	**22**
Type of AEs						
Headache	1 (9%)	2	2 (3%)	5	3 (4%)	7
Vertigo	0 (0%)	0	2 (3%)	4	2 (3%)	4
Musculoskeletal stiffness	1 (9%)	3	0 (0%)	0	1 (1%)	3
Infusion site erythema	0 (0%)	0	2 (3%)	2	2 (3%)	2
Oedema peripheral	0 (0%)	0	1 (2%)	1	1 (1%)	1
Pyrexia	0 (0%)	0	1 (2%)	1	1 (1%)	1
Rigors	0 (0%)	0	1 (2%)	1	1 (1%)	1
Somnolence	0 (0%)	0	1 (2%)	1	1 (1%)	1
Contusion	0 (0%)	0	1 (2%)	1	1 (1%)	1
Pruritus generalized	0 (0%)	0	1 (2%)	1	1 (1%)	1

AE, adverse events.

Discussion

The aim of the studies was to evaluate the FVIII and VWF concentrate (Optivate®) in PTPs. Although the data originate from formal clinical studies, the outcomes represent usual clinical practice; for example, the doses were given to the nearest whole (500 IU) vial.

Combined safety and efficacy data from two similar studies of Optivate® are included in this report. In both these studies, the use of Optivate® was analysed by prophylactic use and on-demand use but, as the patients were not randomized, a comparison is not appropriate. However, the standard management of patients with severe haemophilia A can involve either one of these treatment modalities, and therefore the inclusion of both treatment regimens in the studies allows the clinical utility of Optivate® to be established comprehensively.

The patients using Optivate® prophylactically did not differ in age from those using it on-demand, although only a minority (11/70; 15.7%) were using it prophylactically. Overall, the on-demand patients tended to use lower doses than those in the prophylactic group, both to treat a bleed and as intermittent prophylaxis.

The patients who used Optivate® prophylactically experienced about a third of the number of bleeds as those on-demand, with a bleed rate of 0.24 bleeds per week per patient and 0.75 bleeds per week per patient, respectively. The outcome is in accord with that when the two treatment modalities have been compared [29]. As expected, a majority of Polish patients were treated on-demand and so consumed less FVIII product, compared with those treated in the UK [30].

The efficacy of Optivate® was explored qualitatively by assessing the impact of prophylactic and on-demand treatment on the subjective outcomes of spontaneous bleeds. Physician- and patient-based assessments of response yielded similar positive results.

The data collected on spontaneous bleeding cannot provide evidence of the efficacy of Optivate® relative to other FVIII products, as this was not a comparative study. The results of this study, however, indicate that prophylactic use of Optivate® is effective, with fewer bleeds than with on-demand use.

The use of Optivate® was well tolerated in patients. There were no safety concerns with the use of Optivate® either prophylactically or on-demand. Only seven patients (10%) experienced treatment-related AEs at some time in the long-term follow-up. The number of AEs reported was not unusually high and the types of AEs were comparable to other high-purity products [31]. The most commonly reported treatment-related AEs were headache (4%) and dizziness (3%). The only treatment-related AE experienced by both treatment groups was headache. As the formation of inhibitors currently represents a major obstacle to successful treatment in some patients with haemophilia A, the absence of inhibitors in these trials with Optivate® further supports its use in clinical practice, although all patients were PTPs. The VWF content of Optivate® may have contributed to this outcome.

Conclusions

These findings confirm the clinical safety and efficacy of Optivate® in both the prophylactic management and on-demand treatment of bleeds in patients with severe haemophilia A. Furthermore, no concerns emerged regarding FVIII inhibitors.

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References

1 Rosendaal FR, Smit C, Briet E. Hemophilia treatment in historical perspective: a review of medical and social developments. *Ann Hematol* 1991; **62**: 5–15.

2 Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E. Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. *Ann Intern Med* 1995; **123**: 823–7.

3 Teitel JM. Safety of coagulation factor concentrates. *Haemophilia* 1998; **4**: 393–401.

4 Kernoff PB, Lee CA, Karayiannis P. High risk of non-A non-B hepatitis after a first exposure to volunteer or commercial clotting factor concentrates: effects of prophylactic immune serum globulin. *Br J Haematol* 1985; **60**: 469–79.

5 Carr R. AIDS and haemophilia. *Biomed Pharmacother* 1985; **39**: 347–50.

6 Burnouf T. Safety aspects in the manufacturing of plasma-derived coagulation factor concentrates. *Biologicals* 1992; **20**: 91–100.

7 Barbara JA, Tedder RS. Viral infections transmitted by blood and its products. *Clin Haematol* 1984; **13**: 693–707.

8 Barker LF, Gerety RJ. The clinical problem of hepatitis transmission. *Prog Clin Biol Res* 1976; **11**: 163–82.

9 Teitel JM. Viral safety of haemophilia treatment products. *Ann Med* 2000; **32**: 485–92.

10 Rizza CR, Fletcher ML, Kernoff PB. Confirmation of viral safety of dry heated factor VIII concentrate (8Y) prepared by Bio Products Laboratory (BPL): a report on behalf of U.K. Haemophilia Centre Directors. *Br J Haematol* 1993; **84**: 269–72.

11 Colvin BT, Rizza RC, Hill GH *et al.* Effect of dry-heating of coagulation factor concentrates at 80 degrees C for 72 hours on transmission of non-A, non-B hepatitis. Study Group of the UK Haemophilia Centre Directors on Surveillance of Virus Transmission by Concentrates. *Lancet* 2010 (in press).

12 Thomas D. Clotting factor concentrates - whither purity? *Thromb Haemost* 1995; **74**: 1604–6.

13 Yee TT, Lee CA, Pasi KJ. Life-threatening human parvovirus B19 infection in immunocompetent haemophilia. *Lancet* 1995; **345**: 794–5.

14 Yee TT, Williams MD, Hill FG, Lee CA, Pasi KJ. Absence of inhibitors in previously untreated patients with severe haemophilia A after exposure to a single intermediate purity Factor VIII product. *Thromb Haemost* 1997; **78**: 1027.

15 Pasi KJ, Hill FG. Safety trial of heated factor VIII concentrate (8Y). *Arch Dis Child* 1989; **64**: 1463–7.

16 Brown SA, Dasani H, Collins PW. Long-term follow up of patients treated with intermediate FVIII concentrate BPL 8Y. *Haemophilia* 1998; **4**: 89–93.

17 Kreil TR, Berting A, Kistner O, Kindermann J. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. *Transfusion* 2003; **43**: 1023–28.

18 Remington KM, Trejo SR, Bucznski G *et al.* Inactivation of West Nile, vaccinia virus and viral surrogates for relevant and emergent viral pathogens in plasma-derived products. *Vox Sang* 2004; **87**: 10–8.

19 Darnell MER, Subbarao K, Feinstone SM, Taylor DR. Inactivation of the coronavirus that induces severe acute respiratory syndrome, SARS-CoV. *J Virol Methods* 2004; **121**: 85–91.

20 Dmoszynska A, Hellmann A, Baglin T *et al.* Pharmacokinetics of Optivate®, a high-purity concentrate of factor VIII with von Willebrand factor, in patients with severe haemophilia A. July 10 submitted for publication.

21 Dash C, Gillanders K, Akanezi C, Shaikh-Zaidi R, Hay C. Pharmacokinetics of Optivate®, a high purity, FVIII and VWF concentrate in VWD patients. *Haemophilia* 2010; **16** (Suppl. 4): 35 (08P07).

22 Rosendaal FR, Nieuwenhuis HK, Van Den Berg HM *et al.* A sudden increase in Factor VIII inhibitor development in multitransfused hemophilia A patients in the Netherlands. *Blood* 1993; **81**: 2180–6.

23 Peerlinck K, Arnout J, Di Giambatista M *et al.* Factor VIII inhibitors in previously treated haemophilia A patients with a double virus-inactivated plasma derived factor VIII. *Thromb Haemost* 1997; **77**: 80.

24 Rick ME, Walsh CE, Key NS. Congenital bleeding disorders. *Hematology Am Soc Hematol Educ Program* 2003; 559–74.

25 Laub R, Di Giambattista M, Fondu P *et al.* Inhibitors in German hemophilia A patients treated with a double virus inactivated factor VIII concentrates bind to the C2 domain of the FVIII light chain. *Thromb Haemost* 1999; **81**:39–44.

26 Committee of Medicinal Products for Human use. Notes for guidance to assess efficacy and safety of human plasma derived factor VIII:C and factor IX:C products in clinical studies in haemophiliacs before and after authorisation, London, 2000 (CHMP/BPWG/198/95 rev.1).

27 Hay C, Baglin T, Collins P, Hill F, Keeling D. The diagnosis and management of Factor VIII and IX inhibitors; a guideline from the UK Haemophilia Centre Doctors' Organization (UKHCDO). *Brit J Haematol* 2000; **111**: 78–90.

28 Hay CR, Brown S, Collins P, Keeling D, Liesner R. The diagnosis and management of factor VIII and IX inhibitors; a guideline from the UK Haemophilia Centre Doctors' Organisation. *Brit J Haematol* 2006; **133**: 592–605.

29 Van den Berg HM, Fischer K. Prophylaxis for severe hemophilia: experience from European and the United States. *Sem Thrombos Hemost* 2003; **29**: 49–54.

30 Windyga J, Lopaciuk P, Stefanska E *et al.* Haemophilia in Poland. *Haemophilia* 2006; **12**: 52–57.

31 Committee of Medicinal Products for Human use. Core SPC for human plasma derived and recombinant coagulation factor VIII products, London, 2000. (CHMP/BPWG/1619/99).

