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Special Report

# Recommendations on choice of therapeutic products for the treatment of patients with haemophilia A, haemophilia B and von Willebrand's disease

**UK Regional Haemophilia Centre Directors Committee**

## Contents



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## 1. Objective

The purpose of the fourth edition is to review recent scientific data on coagulation concentrate therapy, and changes in availability, licensing status and pricing structure of therapeutic materials in the context of the recently implemented NHS reforms. The specific recommendations represent the consensus view of the UK Regional Haemophilia Centre Directors, and are intended for the clinical guidance of the UK Haemophilia Centre Directors and/or individual commissioning or purchasing authorities.

## 2. Data on which recommendations are made

Recommendations made prior to the NHS reforms were issued on 16.05.88, 22.05.89 and 01.08.90. They addressed mainly the general issue of blood product safety with respect to transfusion-transmitted viral infections. A possible relationship between product purity and cell-mediated immunity was raised but no clear recommendations made. In the last 18 months, published studies have resolved some outstanding issues, but in terms of providing clear guidelines for therapeutic products, the financial and haemophilia medical audit implications of the NHS reforms assume substantially great importance and cannot be ignored.

### 2.1.1 *Transfusion-transmitted viral infections*

More extensive donor screening procedures and the increasing use of high purity (HP) concentrates combining viral inactivation steps and chromatographic purification procedures have achieved significant risk reduction in the transmission of HIV1, HIV2 and NANB Hepatitis (HCV). Although a small but finite infectious risk is present in donor plasma and thus in cryoprecipitate, ongoing post market surveillance studies of fractionated blood products available in the UK have shown no evidence of viral transmission apart from HBV in isolated cases, indicating the relative efficacy of current virus inactivation procedures. Isolated cases of parvovirus infection have been described, but recent studies undertaken by commercial companies would suggest that chromatographic purification of product is more effective in removing this virus than solvent/detergent (S/D) inactivation, pasteurization or dry-heat treatment.

### 2.1.2 *Purity of coagulation factor concentrates*

Currently, there exists some confusion regarding the definition of purity in blood products, particularly when the degree of purity is correlated to changes in cell-mediated immune parameters. The monoclonal purified products contain almost exclusively the factor VIII:C protein, albeit with trace concentrations of fibrinogen and fibronectin, with a specific activity leaving the chromatography step of $>2\,000$ iu VIII:C/mg protein. To assist the stabilization and administration of these products to patients, albumin, which contains 2–5% impurities, is added, giving a product for infusion with a specific activity of $<10$ iu VIII:C/mg protein.

The ion exchange purified products on the other hand contain the VIII:C-vWF complex with trace concentrations of fibrinogen and fibronectin when eluted from the chromatography columns. These are formulated directly into the final product with or without the addition of albumin, giving a final specific activity $>100$ iu VIII:C/mg protein.

In terms of alterations in cell-mediated immune parameters and purity, the manufacturers of the monoclonal antibody purified products argue that the albumin additive (and its associated human plasma protein contaminants) is inert, and cite Morfini *et al.*,[1] who reported that the induction of immunodeficiency was associated with fibrinogen, fibronectin and immunoglobulin contaminants. On the other hand, the manufacturers of ion exchange purified products state that the major component of the protein content of their factor VIII products is vWF, the physiological stabilizer of VIII:C, and that concentrations of fibrinogen, fibronectin and immunoglobulins are comparable to monoclonal antibody purified products. Until this question is finally resolved by clear product specifications of additional plasma proteins in each batch of factor VIII material, it is convenient to subdivide concentrations into:

A. High Purity (HP) products—prepared by separation procedures involving column chromatographic steps.

B. Intermediate Purity (IP)—products prepared by conventional fractionation methods

### 2.1.3 *H.P. concentrates and cell-mediated immunity*

Chronic alterations in the immune system of haemophilia patients on regular replacement therapy and unrelated to HIV infection have been reported by many investigators, particularly prior to the introduction of heat treated concentrates. Until recently, the hypothesis that HP concentrates induced less alterations in parameters of cell-mediated immunity compared to IP products has evoked considerable debate. Following the initial preliminary studies of Brettler *et al.*,[2] which suggested that HP concentrates stabilized CD4 counts in HIV seropositive haemophilia patients, the following studies have provided support for this view:

(i) Seremitis *et al.*[3] Meta-analysis of two studies compared monoclonal antibody purified HP products to IP material in 80 cases of HIV seropositive haemophilia showed similar findings.
(ii) Fukatake *et al.*,[4] 2 year multicentre trial report demonstrated that monoclonal antibody purified HP factor VIII enhanced cellular immunity in HIV seronegative patients ($n = 54$) and stabilized it in HIV seropositive individuals ($n = 59$) compared with a control group ($n = 46$) on IP product.
(iii) Goldsmith *et al.*[5] Less CD4 decline was shown over a 3 year period with monoclonal antibody purified HP concentrates compared to an IP product.
(iv) de Biasi *et al.*[6] Randomized prospective 2 year trial demonstrated greater CD4 decline in asymptomatic HIV seropositive cases on IP material compared to monoclonal antibody purified HP product.

Two studies, however, do not support the view that product purity may influence immune parameters:

(i) Mannucci *et al.*[7] No difference in immune parameters after 2 years in asymptomatic HIV seropositive patients on IP material ($n = 17$) and on ion exchange purified HP product ($n = 16$).
(ii) Evans *et al.*[8] A 3 year study comparing CD4 counts in previously untreated HIV seronegative haemophilia children ($n = 15$) on IP material (BPL 8Y) with children without haemophilia ($n = 42$). No significant difference was reported. All haemophilia patients were receiving on demand treatment.

### 2.1.4 *Additional components in HP products*

A long-standing concern with monoclonal purified concentrates is that of contaminant murine protein in the final product and the possible clinical effects of chronic administration of such materials to patients. Although various manufacturers compete for the lowest levels of murine proteins in their products, it is clear that any method used in their measurement has a finite limit of sensitivity and that murine proteins are present in all such preparations.

It is far more difficult on the other hand to establish what level of infused murine protein will give rise to clinical problems. Pre-clinical data suggests, that the levels of murine proteins in these products is below the threshold for an immunogenic response. In one manufacturer's post marketing surveillance programme involving the regular administration of monoclonal purified products to 3 000 patients over 3 years, only 24 patients reported adverse reactions such as fever or chills. None of these patients demonstrated detectable levels of circulating murine proteins.

In HP concentrates virus inactivated with the solvent/detergent method, tri- (n-butyl) phosphate (TNBP) and Tween 80 are still present in the final product despite chromatographic purification. Although no data is available of TNBP toxicity in man, weak inhibition of erythrocyte and plasma cholinesterase has been reported.[9] The report[10] that residual TNBP in solvent/detergent treated blood products was about 41 ppm (0.15 mmol/l), has raised concern[11] regarding the potential toxicity of long-term accumulation of TNBP in regularly infused patients receiving such products. The current FDA arbitrary recommendations for safety limits stated for blood products are $< 10$ ppm TNBP and $< 100$ ppm Tween 80.

Sodium thiocyanate is used as a virus inactivation agent and a chaotrope in the production of the monoclonal antibody purified HP factor IX concentrate Mononine®. In the manufacturing procedure, residual viruses are removed after the inactivation step by double virus exclusion ultrafiltration, and the sodium thiocyanate by diafiltration. Thiocyanate is undetectable in the final product using a spectrophotometric assay with a detection limit of 10 μg/ml. Long-term low dosage toxicity data of thiocyanate in humans is unknown although animal data at low dosages shows no evidence of carcinogenesis, mutagenesis or teratogenicity. At the time of writing, over 100 patients have received this product with no reported significant adverse events.

### 2.1.5 *Factor VIII inhibitors and HP concentrates*

Over the past year, concern has been raised regarding the incidence of inhibitors appearing in patients treated with plasma derived monoclonal antibody purified and recombinant factor VIII products. The lack of well controlled studies, differing age groups, previous exposure of patients to blood products and varying types and nature of study concentrates used have complicated the picture.

In previous reports, the incidence of inhibitors was reported as relatively low, 6–8% overall.[12,13] These figures are misleading since patients with all degrees of severity of haemophilia were taken into account. A high incidence of 14.2% overall was later reported by Shapiro *et al.*[14] More recently, however, a prevalence figure of 17.3% was reported from Finland by Rasi *et al.*[15] and the age-dependent cumulative risk of developing an inhibitor before the age of 10 years was 22%. These higher figures are supported by data showing that 70% of inhibitors appear in young patients, with a prevalence of 17.5%[16] and 21%,[17] while one third of inhibitors develop by the age of 4 years and one half by the age of 9 years.[18]

In the various studies of young severely affected

**Table 1.** Factor VIII concentrates in UK

| Product (manufacturer) | LIC. status (type & gener.) donor pool | Viral inact. purification | Sp. act. iu/mg (stabilizer) | Cost* p/iu |
|---|---|---|---|---|
| Monoclate P (Armour) | Full (HP–3) Paid donors | Pasteurization MAb Immunoaffin. Chromatography | 5–10 (> 3 000) (Human serum albumin) | 37–45 |
| 8SM (Kabi contract with BPL— Baxter tech.) | Transitional (named patient for 250 i.u. vials) (HP–3) Voluntary donors | S/D MAb Immunoaffin. Chromatography | 5–10 (> 2 000) (Human serum albumin) | 37–44 |
| Kogenate (Cutter/Bayer) | CTX (HP–4) No donors | S/D Gene insertion MAb Immunoaffin. Chromatography | 5–10 (Human serum albumin) | N/A |
| SNBTS HP VIII (CRTS Lille contract with SNBTS) | CTX named patient (HP–3) Voluntary donors | S/D Ion exchange Chromatography | > 200 None | Central funded free issue |
| Factor VIII VHP (CRTS Lille) | Named patient (CTX pending) (HP–3) Voluntary donors | S/D Ion exchange Chromatography | > 200 None | 30–40 |
| Octavi (Octapharma) | CTX Named patient (HP–3) Paid donors | S/D Ion exchange Chromatography | > 200 None | 30–40 |
| Koate HS (Cutter/Bayer) | CTX (HP–3) Paid donors | S/D Gel exclusion Chromatography | > 150 None | N/A |
| 8Y (BPL) | Full (IP–2) Voluntary donors | Superheat Conventional | < 10 None | 19–24 |
| Z8 (SNBTS) | Full (IP–2) Voluntary donors | H.T. Conventional | < 10 None | Central funded free issue |
| Profilate S.D. (Alpha) | Full (IP–2) Paid donors | S/D Conventional | < 10 None | 16–24 |
| Haemate P (Behring) | Full (IP–2) Paid donors | Pasteurization Conventional | < 10 None | 26–36 |

S/D—solvent/detergent
*cost dependent upon bulk purchase, regional contracts, etc.

patients receiving monoclonal antibody purified factor VIII, the incidence of inhibitors is within the limits expected for the relevant age groups, a view supported by Lusher *et al.*[19] More information is awaited, however, in the recombinant factor VIII (rVIII) PUP trials, where to date eleven of 40 patients on Kogenate® and three of 27 on Recombinate® developed inhibitors. It is of interest, however, that the majority of these inhibitor cases were of low titre, low responding type and could be overwhelmed by increasing the dose of rVIII. Ongoing follow-up of these and other studies is essential to resolve finally the issue of inhibitor development in patients receiving monoclonal antibody purified factor VIII concentrates. A list of available products to treat severe haemophilia patients is shown in Table 1 and products to treat inhibitor patients in Table 4.

### 2.1.6 *IP Factor IX concentrates (PCCs) and thromboembolism*

Recent data collected by the Adverse Events Working

**Table 2.** Factor IX concentrates in UK

| Product (manufacturer) | LIC. status (type & gener.) donor pool | Viral inact. purification | Sp. act. iu/mg (stabilizer) | Cost* p/iu |
|---|---|---|---|---|
| Defix (SNBTS) | Full (IP–1) Voluntary donors | H.T. Conventional | < 10 None | Central funded free issue |
| 9A (BPL) | Transitional (IP–2) Voluntary donors | Superheat Conventional | < 10 None | 26–27 |
| Factor IX VHP (CRTS Lille) | Named patient (HP–3) Voluntary donors | S/D Ion exchange Chromatography | > 100 None | 30–40 |
| Mononine (Armour) | CTX (HP–3) Paid donors | Sodium thiocynate MAb Immunoaffin. Chromatography | > 200 None | N/A |
| Alpha Nine (Alpha) | CTX (HP–3) Paid donors | S/D Ion exchange Chromatography | > 200 None | N/A |

S/D—solvent/detergent
*cost dependent upon bulk purchase, regional contracts, etc.

Party has shown that over the past 2½ years, eight cases of thromboembolism have occurred in patients with severe factor IX deficiency undergoing surgery with high-dose PCC cover (NHS 9A and DEFIX). These IP concentrates contain additionally factors X and II. Acting on this information, recommendations were circulated advocating the use of HP factor IX concentrates in acute or elective surgery involving such cases. This recommendation was based upon a report indicating the lower thrombogenic potential of HP concentrates compared to PCCs,[20] and subsequently supported by clinical trial data.[21] Although no case of thromboembolism of clinical significance in non-surgical factor IX deficient patients receiving replacement therapy alone has yet to be reported with the current BPL or SNBTS PCC concentrates, the potential thrombogenic nature of these products raises the issue that a progressive transition from NHS 9A and DEFIX to HP factor IX concentrates is warranted. A continuing role for PCC concentrates would be for the occasional case in oral anticoagulant reversal where constraints of circulatory overload are of clinical significance, and in the management of symptomatic factor X deficient patients. A list of available products to treat factor IX deficiency is shown in Table 2.

### 2.1.7 *Concentrates for the management of von Willebrands Disease (vWD)*

For many years, even with the recognition of transfusion transmitted viral infections in untreated plasma derivatives, cryoprecipitate has been used for the management of symptomatic vWD when DDAVP has been considered inappropriate or non-efficacious. The continued use of such material is highly questionable when ample documentation exists that specific viral-inactivated concentrates are available and effective. It would seem appropriate that the use of cryoprecipitate be discontinued. In vWD, viral inactivated concentrates shown to be effective include BPL 8Y,[22,23] Hemate P[24] or high purity vWF concentrate (vWF VHP) CRTS Lille.[25] It has been noted, however, that in some subtypes of vWD, IP products have been reported anecdotally to be less effective than HP concentrates possibly reflecting the heterogeneity of the disorder as well as batch to batch variations in the biological efficacy of vWF in IP materials. A list of available products to treat DDAVP unresponsive vWD is shown in Table 3.

### 2.1.8 *Concentrates for the management of factor VIII/IX inhibitors*

The clinical management of inhibitor patients is complex, and many therapeutic regimens have been devised depending on antibody titre, type of anamnestic response and treatment objective (symptomatic management or antibody eradication). No one form of treatment has been shown to be uniformly effective, and therapeutic alternatives are diverse and expensive. A list of available therapeutic products is shown in Table 4.

**Table 3.** Concentrates for the management of vWD

| Product (manufacturer) | LIC. status (type & gener.) donor pool | Viral inact. purification | Sp. act. iu/mg (RCoF) (stabilizer) | Cost* p/iu |
|---|---|---|---|---|
| Haemate P (Behring) | Full (IP–2) Paid donors (plasma brokerage) | Pasteurization Conventional | < 10 None | 26–36 |
| 8Y (BPL) | Full (IP–2) Voluntary donors | Superheat Conventional | < 10 None | 19–24 |
| vWF VHP (CRTS Lille) | Named patient (HP–3) Voluntary donors | S/D Ion exchange Chromatography | > 200 None | 30–40 |

S/D—solvent/detergent
*cost dependent upon bulk purchase, regional contracts, etc.

**Table 4.** Concentrates for FVIII/IX inhibitor management excluding human FVIII products

| Product (manufacturer) | LIC. status (type & gener.) donor pool | Viral inact. purification | Sp. act. iu/mg (stabilizer) | Cost* p/iu |
|---|---|---|---|---|
| Hyate C (Porton/ Speywood) | Full (HP) Animal product | N/A P.E. Chromatography | N/A None | 78 + VAT |
| FEIBA (Immuno) | Named patient N/A (IP) Paid donors | Steam/pressure Conventional | N/A None | 38 |
| Autoplex (Baxter) | Named patient N/A/(IP) Paid donors | S/D Conventional | N/A None | 75 |
| Acset (CNTS, Paris) | Named patient N/A (HP) Voluntary donors | S/D Ion exchange Chromatography | N/A None | 30–40 |
| rVIIa (Novo Nordisk) | Compassionate use (HP–4) No donors | S/D Gene insertion MAb Immunoaffin. purification | N/A None | Free of charge |

S/D—solvent/detergent
*cost dependent upon bulk purchase, regional contracts, etc.

## 3. High purity therapeutic products currently available in UK

In previous editions of these recommendations, available therapeutic products have been reviewed in detail. Concentrates currently used for various bleeding disorders are listed in tabular form with details of donor pool, manufacturing method, specific activity and price (Tables 1–4). Some comment, however, should be made on a few newly introduced products either with full product licences, transitional product licences, on clinical trial exemption certificates or on a named patient prescription basis. The list of these products is not exhaustive since additional concentrates will soon become available (e.g., Alpha VIII, Nanotiv etc.).

### *3.1.1*

*Monoclate P* is a monoclonal antibody purified pasteurized high purity factor VIII preparation:

—derived from paid donor plasma obtained from the USA from the manufacturer's wholly owned collection facility.
—plasma screened for antibodies to HIV1, HIV2 and HCV and also for elevated levels of ALT.
—contains little vWF.
—has full product licence.
—has been assessed extensively in clinical trials and in post marketing surveillance studies.
—is considered safe and efficacious (despite previous concerns discussed in 2.1.4 and 2.1.5).

*3.1.2*

*BPL 8SM* (Bio Products Ltd., Elstree, Herts.) is a monoclonal antibody purified, solvent detergent inactivated high purity factor VIII preparation:

—derived from volunteer donor plasma obtained from England and Wales through the BTS.
—plasma screened for HIV1, HIV2 and for HCV following the full introduction of HCV testing by the BTS.
—technology transfer from Baxter Healthcare to BPL.
—current contract fractionation of English plasma by Kabi in Stockholm, Sweden.
—contains little vWF.
—no clinical trials performed on this product (as 8SM) in the UK before its introduction with a transitional product licence.
—used for 3–4 years as the equivalent product Hemofil M in other countries, and considered as safe and efficacious as other monoclonal antibody purified fully licensed HP products (despite previous concerns discussed in 2.1.4 and 2.1.5).
—250 i.u. vials not currently available, but when introduced will be on a named patient prescription basis.

*3.1.3*

*SNBTS HP VIII* (Scottish National Blood Transfusion Service, Edinburgh, Scotland) is an ion exchange chromatography purified solvent detergent inactivated high purity product:

—derived from volunteer donor plasma from Scotland and Northern Ireland through the SNBTS.
—plasma screened for HIV1, HIV2 and HCV.
—technology transfer with CRTS Lille (Centre Regional Transfusion de Sanguine de Lille) France.
—contains VIII:C-vWF complex.
—current clinical trials under CTX in progress in Scotland and Northern Ireland.
—available outside the clinical trials on named patient basis.
—has been used for 3–4 years in France for routine patient management in haemophilia as CRTS factor VIII VHP (derived from volunteer donor plasma in France) without reported viral transmission event.
—considered safe and efficacious.
—due to replace Z8 in 1992.
—SNBTS HP factor VIII essentially identical to CRTS factor VIII VHP.
—some similarity to Octapharma's product (Octavi) although Octavi manufactured from paid donor plasma obtained on a plasma brokerage basis.

*3.1.4*

*CRTS vWF VHP* is an ion exchange chromatography purified, solvent detergent inactivated high purity concentrate:

—derived from volunteer donor plasma in France.
—plasma screened for antibodies to HIV1, HIV2 and HCV and also for elevated levels of ALT.
—contains little or no VIII:C protein.
—effective in symptomatic vWD.
—available on named patient basis.

*3.1.5*

*CRTS F.IX VHP* is an ion exchange chromatography purified solvent detergent inactivated high purity factor IX concentrate:

—derived from volunteer donor plasma in France.
—plasma screened for antibodies to HIV1, HIV2, and HCV and also for elevated levels of ALT.
—contains no factors VII, X, II or Protein C but some heparin.
—has been used for 2–3 years in France for routine patient management without significant adverse events.
—some similarity to Octanyne (Octapharma), although Octanyne manufactured from paid donor plasma obtained on a plasma brokerage basis.
—available on named patient basis.

*3.1.6*

*Mononine* is a monoclonal antibody purified high purity factor IX concentrate virus inactivated by sodium thiocyanate and virus exclusion membrane filtration:

—derived from paid donor plasma in the USA (see Monoclate P).
—plasma screened for antibodies to HIV1, HIV2, and HCV and also for elevated levels of ALT.
—contains no factors VII, X, II, Protein C or heparin.
—over 100 patients have been treated in clinical trials in the USA without adverse events.
—current trials in the UK as US IND.

*Alpha Nine* is an ion exchange chromatography purified solvent detergent inactivated high purity factor IX concentrate:

—derived from paid donor plasma obtained from USA.
—plasma screened for antibodies to HIV1, HIV2

and HCV and also for elevated levels of ALT.
—contains trace concentrations of factor X and also heparin.
—current clinical trials on CTX in UK.
—prefilled syringe or vial presentation.

## 4. NHS reforms

### 4.1.1 *National Health Service Community Care Act 1990*

Following the implementation of this Act in April 1991, haemophilia care has been thrown open to market forces. Very little provision and protection was offered in the Act for patient groups such as those with haemophilia and other related haemostatic disorders, where numbers are relatively few, the nature of the disorder with on demand therapy is progressive, and treatment costs are high and recurring.

### 4.1.2 *Devolvement of costs to DHAs (District Health Authorities)*

In April 1991, most DHAs assumed, for the first time, the responsibility, both administratively and financially, for the provision of care to their residents with haemophilia. Commissioners in DHAs have requested details of the current service, quality of care measures and expenditure to project future cost implications relevant to the continued purchase of services. Budgetary devolvement for haemophilia services in many DHAs has led to financial shortfalls, which could lead to the future commissioning of services with lower levels of provider activity and quality standards. Such potential developments could constrain the implementation of therapeutic recommendations and undermine the essential principles of clinical audit. The UK Haemophilia Society, in an attempt to resolve this, has circulated *'Essentials of Haemophilia Care'* which recommends rationalization of care to centres with high quality standards.

### 4.1.3 *Abolition of Crown Immunity in the NHS*

Under Schedule 8, paragraph 14 of the NHS Community Care Act, Crown Immunity has been removed from health service bodies within the NHS, such as BPL and the Plasma Fractionation Centre of the SNBTS. These organizations are now subject to the provisions of the Medicines Act 1968. In the case of BPL (not SNBTS), the transitional arrangements specified in the NHS Act 1990 have been utilized, to ensure that BPL can become subject to the Medicines Act in an orderly manner. Thus BPL can continue to pursue its activities which were current prior to April 1991 under Crown Immunity, but new activity must conform to the regulations of the Medicines Act. Under these transitional arrangements BPL submitted data on the high purity 8SM product (500 and 1 000 iu vials), and was granted transitional product licences, which will be assessed at a later state for full product licence suitability. In contrast, the SNBTS have chosen to follow stringently the regulations of the Medicines Act 1968 and pursue full licensing through clinical trials (CTX) and prescription outside the clinical trials on a named patient basis.

### 4.2.1 *Current UK licensing regulations of blood products*

At the present time, the following regulations apply to blood products:

(i) Full product licence—subject to the regulations, and issued by the UK MCA (Medicines Control Agency).
(ii) Transitional product licence—see 4.1.3 as part of NHS Community Care Act 1990.
(iii) Clinical Trial Certificate (CTC).
(iv) Clinical Trial Exemption Certificate (CTX)–SI 1981 No 164–liability rests with manufacturer during the pursuit of clinical trials of these unlicensed products. The protocols for CTC and CTX trials must be approved by MCA.
(v) named patient prescription–89/341/EEC–SI 1972 No 1200–liability usually rests with the physician who prescribes the use of these unlicensed products.

## 5. Therapeutic recommendations

The scientific and medical evidence is now sufficiently well established to merit a change in therapeutic policy for the management of patients with haemophilia A and B and vWD. This document lays out general and specific recommendations for this purpose.

### 5.1.1 *General Recommendations*

(i) *Hepatitis B vaccination.* All patients, who are seronegative to hepatitis B, and are either receiving blood products or could be considered, because of their medical condition, to be eligible for blood product therapy at any stage, should be immunized against hepatitis B. Such patients require regular follow-up of their hepatitis B immune status and revaccination when appropriate.

(ii) *Use of DDAVP.* All patients with moderate/mild haemophilia and mild vWD should be assessed for response to DDAVP preferably as part of their initial assessment. In such patients, defined efficacy of DDAVP therapy would be highly cost-effective man-

agement, and reduced the risks of unnecessary exposure of such patients to blood product therapy.

(iii) *Discontinued use of Cryoprecipitate.* In view of the potential virus transmission from cryoprecipitate, it is recommended that specific virus inactivated concentrates be used in the management of von Willebrand's Disease (see Table 3) and in any other conditions where therapy with such untreated material would be considered justified and treated concentrates are available.

5.1.2 *Specific Recommendations*

(i) *HIV antibody positive patients.* In HIV seropositive haemophilia patients requiring blood product therapy, high purity (HP) factor VIII/IX products should replace IP materials to restrict immunosuppression.

(ii) *HIV antibody negative patients.* In HIV seronegative haemophilia patients requiring blood product therapy, current evidence on HP products from several clinical trials and post marketing surveillance studies, following the administration of hundreds of millions of units, indicates that these products are safe from virus transmission and are highly efficacious. Although similar data are available for BPL 8Y, SNBTS Z8, and other licensed IP products, there is evidence to indicate that the essential chromatographic steps employed in the manufacture of current HP materials confer an additional margin of safety and less immune modulation. Other considerations related to the very low concentrations of allogeneic proteins in HP products, the small volume required for infusion due to their improved solubility, and the relative absence of allergic side-effects following their administration add further support for their use as blood products of choice. For these reasons, the transition from IP products to HP concentrates is recommended in HIV seronegative patients with haemophilia with appropriate surveillance of safety and efficacy. This will permit inclusion of data from the prospective clinical trials currently pursued by Scottish and N. Irish Haemophilia Centre Directors using HP factor VIII manufactured by the SNBTS, and facilitate the collation of UK wide scientific data for HP product evaluation.

(iii) *Patients with factor IX deficiencies.* In all patients with factor IX deficiency requiring blood product therapy, it is recommended that HP factor IX concentrates be adopted as soon as practically possible within the constraints of availability and licensing. Patients with mild factor IX deficiencies undergoing surgery should be treated with HP factor IX concentrates in preference to fresh frozen plasma.

(iv) *Patients with vWD.* For the management of symptomatic vWD, it is recommended that IP concentrates should be progressively replaced by more specific HP materials subject to the assessment of data from ongoing clinical trials.

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