

## Factor VIII Treatment/Supply to Patients with Haemophilia and von Willebrands Disorder

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**Author Branch** Clinical Policy

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**Applies to** Area Health Services/Chief Executive Governed Statutory Health Corporation, Board Governed Statutory Health Corporations, Affiliated Health Organisations, Community Health Centres, Dental Schools and Clinics, Divisions of General Practice, Government Medical Officers, NSW Ambulance Service, Private Hospitals and Day Procedure Centres, Public Health Units, Public Hospitals

**Distributed to** Public Health System, Community Health Centres, Dental Schools and Clinics, Divisions of General Practice, Government Medical Officers, Health Associations Unions, Health Professional Associations and Related Organisations, NSW Ambulance Service, Public Health Units, Public Hospitals, Private Hospitals and Day Procedure Centres, Tertiary Education Institutes

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**CIRCULAR**

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<b>Contact</b>	Mr G Mulheron (02) 9391 9465 Centre for Research and Clinical Policy

**Treatment and Supply of Factor VIII to Patients with Haemophilia and von Willebrands Disorder****Purpose of this circular:**

1. To replace circular No.76/1, and amend the Patient Matters Manual.
2. To provide an update on action recently taken to focus more attention on improvements to services for patients with haemophilia.
3. To request that copies of this circular be made available to all staff likely to come into contact with patients with haemophilia or carriers of the haemophilia gene, especially staff working in haematology, obstetrics, genetic counselling, orthopaedic, general and dental surgery and emergency medicine.

**Review of Haemophilia Services**

Following a decision by the Australian Health Ministers Advisory Council to take action to improve the health outcomes for people with haemophilia, it was decided to set up at least one haemophilia comprehensive care centre in each State of Australia.

NSW Health then appointed a working Party to review the provision of haemophilia care services in NSW and approval was subsequently given to :-

- Establishment of the Haemophilia Advisory Council of NSW & ACT incorporating a Clinical Committee to replace the Haemophilia Advisory Group.
- Utilising a network of hospitals and services in NSW and Canberra for the provision of treatment and care through a three tier system of primary, secondary and tertiary level services.
- Granting provisional designation as a tertiary level haemophilia treatment centre to six haemophilia units at Royal Alexandra Hospital for Children (New Childrens Hospital), Westmead Hospital, Royal Prince Alfred Hospital, Prince of Wales Hospital / Sydney Childrens Hospital, Mater Misericordiae Hospital Newcastle (Waratah) and Canberra Hospital.

Distributed in accordance with circular list(s):

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## **Setting up the Haemophilia Advisory Council of NSW & ACT**

The Council commenced operation in July 1998 and defined 6 key focus areas on which it would concentrate as follows:-

1. High Cost Blood Products
2. Clinical Policy
3. Haemophilia Care Model
4. Register and Database
5. Information/ Education/ Training
6. Research

In summary, the Council is to develop over the next two years, a Haemophilia Care Plan for NSW. As major by-products or components of this plan, the Council will manage the budget for purchase of recombinant Factor VIII, review existing and develop new clinical policy, set up a register and database to assist decision-making, develop information education and training resources and consider the priorities for research.

## **Amendments to Patient Matters Manual and Circulars**

As a first step, information in the Patient Matters Manual was reviewed. Previously, two circulars and a Guideline have been issued that relate to the haemophilia services or treatment:-

Circular 76/1 - Surgery for Haemophilia Patients.

Circular 97/34 - Guidelines on Factor VIII usage.

Patient Matters Manual - Guidelines for use of Plasma Component Therapy.

Circular 76/1 is hereby rescinded and replaced by this circular. The Haemophilia Therapy Review Group has now been replaced by the Clinical Committee of the Haemophilia Advisory Council of NSW & ACT, which carries out the same functions as the Review Group did, but has several new functions. Essentially the Clinical Committee allocates the appropriate amount of Factor VIII and determines priorities for elective surgery consistent with the surgical need and medical status of the patient, maintains surveillance of the available supplies of blood clotting products, maintains a priority list for elective surgery and advises on clinical policy for the treatment of people with haemophilia.

The previous implied policy that all surgery on patients with haemophilia should be undertaken in one of the Designated Centres has been strongly confirmed. Units outside of the Provisionally Designated Centres should maintain referral links to these Centres for the purposes of elective surgery, supply of clotting factor and specialist treatment.

Applications for the supply of Factor VIII for elective surgery to be undertaken in one of the Designated Centres should be submitted in the first instance to the Executive Officer, Haemophilia Advisory Council, Level 7, NSW Health Department, LMB 961, North Sydney, 2059. Consideration will be then given to the request by the Clinical Committee of the Advisory Council.

Applications for the supply of Factor VIII for elective surgery and placement on the elective surgery priority list should be submitted in an envelope marked Confidential using the form attached to this circular.

The Guidelines for Factor VIII Usage in circular 97/34 are still in force but currently under review by an Australian Health Minister's Advisory Council Review Committee. The Guidelines for Plasma Component Therapy have been replaced by the attached amendment which only omits the final paragraph of the former document.

In addition the 1997 Haemophilia Foundation of Australia's document *Guidelines on Therapeutic Products to Treat Haemophilia and other Hereditary Coagulation Disorders in Australia* is attached for information.

### **Summary of Amendments and Release of Future Information**

The Patient Matters Manual will be amended by

- (1) omitting circular 76/1 and the former Guidelines for Plasma Component Therapy.
- (2) inserting this circular, with the new Guidelines for Plasma Component Therapy and the Guidelines on Therapeutic Products to Treat Haemophilia and other Coagulation Disorders in Australia.

Circular 97/34 will be retained pending the results of the Commonwealth Health Department's Factor VIII Review, and further advice will be issued as the haemophilia care plan is developed.

### **Comments Sought from Staff**

Should there be any aspects of haemophilia care that health workers wish to comment on, or bring to the attention of the Haemophilia Advisory Council, I would encourage them to do so by writing to Gary Mulheron, Executive Officer, Haemophilia Advisory Council of NSW and ACT, LMB 961, North Sydney, NSW 2059, or by sending a fax on (02) 9391 9232 or by email at [gmulh@doh.health.nsw.gov.au](mailto:gmulh@doh.health.nsw.gov.au)

Michael Reid  
**Director General**

**HAEMOPHILIA ADVISORY COUNCIL of NSW & ACT**  
**Application for the supply of Factor VIII for elective surgery**

Elective surgery involving people with a haemophilia related co-diagnosis should almost invariably be undertaken at one of the Designated Haemophilia Centres. It is recommended that all applicants read Circular 2000/23 before submitting this application.

This application for the supply of the clotting factor required for elective surgery should be submitted in the first instance to the address below. Consideration will be then given to the request by the Clinical Committee of the Advisory Council at its next available meeting.

Depending on urgency and stocks of clotting factor, elective surgery may have to be deferred and be subject to the haemophilia elective surgery priority list.

**Patient-s Name:**.....**Date of birth**.....  
(dd/mm/yy)

**Weight :** ..... **Haemophilia / von Willebrands Type :** .....  
(Kgs)

**Factor Level :**..... **Inhibitor Status:**.....

**Indications for Surgery :**.....  
.....  
.....  
.....

**Proposed Hospital/Location of Surgery :**.....

**Surgery proposed :**.....

**Degree of Urgency:**.....

**Estimated AHF Requirement:**.....bottles or.....IUs

**Proposed Date of Surgery :**..... **For Bolus "** or **Continuous Infusion "**  
(dd/mm/yy)

**Is Patient on Recombinant Factor VIII "** or **Plasma-Derived AHF "**

**Nature of any complicating conditions :**.....  
.....

Signed: ..... Title: ..... Date .....  
(Applicant)

Please place this application in an envelope marked Confidential and addressed to :

The Executive Officer, Haemophilia Advisory Council  
Centre for Research and Clinical Policy  
Level 7, NSW Health Department  
LMB 961  
**NORTH SYDNEY NSW 2059**

**HAEMOPHILIA ADVISORY COUNCIL of NSW & ACT**  
**Approval for the supply of Factor VIII for elective surgery**

**1. Further Information to be sought.....**

.....

.....

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.....

.....

**2. From: .....**

**3. Details of further Information Obtained:.....**

.....

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**4. Decision of the Clinical Committee:.....**

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.....

.....

**5. Signed:..... Date .....**

**6. Approved - ARCBS to supply product "**

or

**Deferred - to Haemophilia Elective Surgery / Factor VIII Waiting list "**

or

**Not Approved - for following reason(s)**

.....

.....

.....

.....

### 24.3.1 GUIDELINES ON THE USE OF PLASMA COMPONENT THERAPY IN HAEMOPHILIA AND VON WILLEBRAND'S DISEASE

These guidelines have been prepared by the Haemophilia Therapy Review Committee of NSW for use by General Practitioners in the treatment of acute bleeding episodes in patients with Factor VIII or IX deficiencies. They are a guide to initiate treatment for bleeding in these patients while contacting the appropriate Haemophilia Treatment Centre in one of the Teaching hospitals in Sydney or Newcastle. It is assumed in these notes that the diagnosis of the underlying coagulation defect had been made and the defect severity ascertained. It is imperative that any one with a suspected haemostatic defect be referred to a major centre for diagnosis and co-ordinated interdisciplinary care. This will allow for correct management of bleeding episodes.

#### HAEMOPHILIA A

(Factor VIII coagulant deficiency)

Most medical problems are related either directly or indirectly to spontaneous or post-traumatic episodes of bleeding. This bleeding occurs into joints, particularly those bearing weight, into soft tissues such as muscle or retroperitoneal areas, into the urinary tract or following dental or surgical procedures if the patient is inadequately treated with replacement factors. Any symptoms in a patient with haemophilia should be considered due to bleeding unless proved otherwise.

Management: It is well established that prompt and adequate replacement of factor VIII is the cornerstone to therapy. It is recognised that the average normal individual has 1 unit of Factor VIIIc activity per ml of plasma, i.e., 2500 units of Factor VIIIc for an average volume of 2500 mls of plasma which represents 100% activity (normal range 50-150%).

Patients with Factor VIIIc deficiency can be classified as:

severe - less than 1% Factor VIIIc activity

moderate - 1-5% Factor VIIIc activity

mild - 5-30% Factor VIIIc activity

Plasma component therapy available

Cryoprecipitate: contains 100 units of Factor VIIIc per bag.

Factor VIII concentrate: each vial contains between 200-400 units of Factor VIIIc. The amount is stated on the label.

Fresh frozen plasma: 100-200 units of Factor VIIIc in 200-250ml of plasma.

Factor VIII levels in therapy

<u>Indications for treatment</u>		<u>Duration of treatment (Days)</u>
<u>Factor VIIIc levels (%) required</u>		
Haemarthrosis	30 (0.3u/dl)	1-2
Haematoma	30 (0.3u/dl)	2
Trauma	30 - 50 (0.3-0.5u/dl)	2
Haematuria	30 (0.3u/dl)	2
Dental extraction	100 (1.0u/dl)	2
Surgery	100 (1.0u/dl)	3
	then 50 (0.5u/dl)	for a further 4

Dose calculation using plasma volume

Aim for Factor VIIIc elevation to 30%; use cryoprecipitate or Factor VIII concentrate. In a severe haemophiliac with less than 1%

activity, the initial dose would be  $\frac{30 \times 2500 \text{ units}}{100} = 750 \text{ units}$  (or 800 units) assuming plasma volume of 2500mls.

In a mild haemophiliac with Factor VIIIc activity of say 8%, the

initial dose would be  $\frac{(30-8) \times 2500 \text{ units}}{100} = 550 \text{ units}$  (or 600 units) assuming plasma volume of 2500 mls. Give the initial calculated dose and follow up with half the initial dose at 12 hourly intervals.

Dose calculation using weight

Infuse one unit of Factor VIIIc/kg for every two percentage point increase in plasma VIIIc desired. Aim for a Factor VIIIc elevation of 30%; use cryoprecipitate or Factor VIII concentrate. In a severe haemophiliac with less than 1% activity, the initial dose would be

$\frac{30}{2}$

$\times 60 = 900 \text{ units}$  assuming a body weight of 60kg. In a mild haemophiliac with Factor VIIIc activity of 8%, the initial dose would be

$\frac{(30-8)}{2}$

$\times 60 = 660 \text{ units}$  (or 700 units) assuming a body weight of 60kg. Give the initial calculated dose and follow up with half the initial dose at 12 hourly intervals.

Other agents

DDAVP. (Desmopressin), antifibrinolytic agents and prothrombinex may be of value in the management of Factor VIIIc deficiency. These agents should be used only on the advice of the haematologist in the Haemophilia Treatment Centres.

Inhibitors: Ten percent of patients with haemophilia develop inhibitors. This presents a difficult management problem. These patients must be referred to the appropriate Haemophilia Treatment Centre.

Dental extraction: Contact the appropriate Haemophilia Treatment Centre for advice. It is preferable to perform this procedure in a Haemophilia Treatment Centre.

Emergency surgery: Contact the appropriate Haemophilia Treatment Centre for advice in the first instance. Note that emergency surgery outside a Haemophilia treatment Centre is unsafe.

Elective surgery: The Haemophilia Therapy Review Committee reviews all cases requiring elective surgery and schedules the order of priority for surgery according to the need of the patient and available supply of Factor VIII. Any surgical procedure on these patients outside a Haemophilia Treatment Centre is unsafe.

## HAEMOPHILIA B

### (Factor IXc deficiency, Christmas disease)

Most medical problems are related directly or indirectly to spontaneous or post-traumatic episodes of bleeding. (see Haemophilia A).

Management: Prompt and adequate replacement of Factor IX is the cornerstone of therapy. It is recognised that the average normal individual has 1 unit of Factor IXc activity per ml of plasma, i.e. 2500 units of Factor IXc for an average volume of 2500 mls of plasma which represents 100% activity (normal range 50 - 100%).

Patients with Factor IXc deficiency can be classified as:

- severe - less than 1% Factor IXc activity
- moderate - 1-5% Factor IXc activity
- mild - 5-30% Factor IXc activity

#### Plasma component therapy available

Prothrombinex: Contains about 1000 units each of Factor II, IX, X. About 30-50% of the Factor IX is activated which means that it is rapidly cleared from the circulation after infusion leaving an effective infusion level of 600 units per vial.

Fresh frozen plasma: 100-200 units of Factor IXc in 175-200mls of plasma.

#### Factor IX levels in therapy

Similar to needs of Factor VIIIc levels, see previous table.

#### Dose calculation using plasma volume

See formula used for determining Factor VIIIx dose. Aim for a Factor IXc elevation to 30%, use Prothrombinex assuming an effective concentration of 600 units per vial. In a person with a Factor IXc level of 10%, elevation to 30% requires  $\frac{(30-10) \times 2500}{100} = 500$  units.

#### Dose calculation using weight

See formula used for determining Factor VIIIc dose. Aim for a further IXc elevation to 30%, use Prothrombinex assuming an effective level of 600 units per vial.

Inhibitors, dental extraction, surgery Contact the appropriate Haemophilia Treatment Centre for advice.

## VON WILLEBRAND'S DISEASE

The primary disorder in Von Willebrand's disease is a quantitative or qualitative abnormality of the Factor VIII molecule. Poor platelet adhesion and a low Factor VIIIc level cause the bleeding. A number of genetic variables have been described, but these, although important in the recognition of this disease, can be ignored in the management of bleeding. In Von Willebrand's disease, excess bleeding from lesions in the nose or mouth or skin cuts and menorrhagia is common. The joint and muscle haemorrhages so characteristic of haemophilia A and B are not seen unless the patient has major trauma or a severe form of the disease. Bruising is a common feature of Von Willebrand's disease, but by itself does not require treatment.

### Therapy available

DDAVP (desmopressin) used in mild to moderate bleeding. Contact the appropriate Haemophilia Therapy Centre for advice.

Cryoprecipitate: Treatment of choice in severe haemorrhage.

Factor VIIIc is also effective.

### Dose calculation

The aim is to give 'normal' Von Willebrand factor assuming its total absence to correct the poor platelet adhesion and simultaneously achieve a Factor VIIIc level to above 50%. Therefore, ascertain the usual level of Factor VIIIc in the patient. To replace Von Willebrand's Factor, give 10 units of Factor VIII/kg body weight as cryoprecipitate. (e.g., 60/kg give 600 units). Calculate the resulting level of Factor VIIIc achieved as described for Haemophilia A using either plasma volume or body weight. Supplement with more Factor VIIIc if a calculated level below 50% obtained, (this is rarely necessary). Give cryoprecipitate 12 hourly for one day and once daily thereafter until haemorrhage is controlled.

Dental extraction, surgery: Contact the appropriate Haemophilia Treatment Centre for advice.

#### Complications of plasma component therapy

Allergic reactions; Erythema, bronchospasm, oedema are the more common manifestations. Parenteral anti-histamines and/or steroids are useful.

Hepatitis: Immunization of children against hepatitis B is advisable. Adults should be checked for the presence of antibody before immunization. If Hepatitis B antigen is positive, immunization is not required. Blood donors are screened for hepatitis B antigen. Nevertheless, the risk of non A non B remains present, whilst hepatitis B transmission is rare.

AIDS: Blood donors are carefully selected and all donations are screened for the presence of antibody against HIV. Plasma and its concentrates are heat treated to inactivate the virus.

Immune Dysfunction: Patients receiving plasma or component therapy develop abnormalities of T lymphocytes function. The clinical significance of these abnormalities remains to be elucidated.

Circulatory overload: May occur when large volumes of fresh frozen plasma is used, particularly in small children.

**GUIDELINES ON  
THERAPEUTIC PRODUCTS  
TO TREAT HAEMOPHILIA  
AND OTHER HEREDITARY  
COAGULATION DISORDERS  
IN AUSTRALIA**

J V Lloyd  
Chairman  
HFA Medical Advisory Panel  
March 2000

# **GUIDELINES ON THERAPEUTIC PRODUCTS TO TREAT HAEMOPHILIA AND OTHER HEREDITARY COAGULATION DISORDERS IN AUSTRALIA**

In 1997 the Haemophilia Foundation Australia (HFA) Medical Advisory Panel adopted, with minor modifications for Australian use, this document which had been developed by the *United Kingdom Haemophilia Centre Directors Organisation Executive Committee*, and published in the journal *Haemophilia* (1997) 3, 63-77. This edition contains further minor revisions by the Medical Advisory Panel, current as of March 2000.

## **1. Introduction**

There have been significant developments in coagulation factor concentrates for treating haemophilia and other hereditary coagulopathies. Recombinant concentrates are now in use and new recombinant products are under clinical trial. Therefore in 1997 the United Kingdom Haemophilia Centre Directors Organisation (UKHCDO) prepared substantially revised guidelines to replace their previous recommendations [1]. The recommendations are consistent with those prepared under the auspices of the World Health Organisation [2], National Hemophilia Foundation (USA) [3] and other European countries [4].

These guidelines offer advice on the choice of therapeutic products and are based on the best published scientific and medical information. This version of the guidelines will be reviewed regularly by the Medical Advisory Panel.

Currently unlicensed coagulation factor concentrates may become licensed in the near future and these guidelines have therefore also included products available at present only on a 'named patient basis'. As treatment is expensive it is important to ensure that limited resources are used optimally whilst not compromising safety. Guidance is given as to which of the recommendations should be current practice and which can be enacted when resources allow. To ensure that treatment arrangements are appropriate clinical audits should be a regular feature of all Haemophilia Centre activities; suggestions for this are given in these guidelines.

## **2. Methods**

The UK guidelines were drafted by a Task Force appointed by the UKHCDO Executive Committee and circulated widely for consultation. Relevant scientific papers were identified from Medline using the index terms haemophilia, therapy, hepatitis, HIV, parvovirus, Creutzfeld-Jakob disease, immune and thrombosis [5]. Recommendations have been based on reports with the highest levels of evidence (Appendix 1). Members of the Task Force made a declaration of interest to the former Chairman, UKHCDO. This version of the guidelines was modified from the UK guidelines in 1997 by the HFA Medical Advisory Panel, and revised in March 2000.

## **3. Fresh plasma products currently not virally inactivated**

### **3.1. Fresh plasma products**

None of these products is currently virally inactivated.

*3.1.1. Fresh frozen plasma (FFP).* This is prepared from whole blood by cold centrifugation; the plasma is rapidly frozen in a liquid nitrogen, or mechanical freezer.

*3.1.2. Cryoprecipitate.* This is prepared from FFP by slow thaw over 24 h at 4 °C, the cold insoluble precipitate, cryoprecipitate, is separated by centrifugation.

## **4. Manufacture of therapeutic coagulation factor concentrates**

### **4.1. Factor VIII concentrates**

Plasma-derived FVIII concentrate is manufactured from cryoprecipitate by a variety of fractionation techniques. These include three main groups: conventionally purified, ion exchange or heparin affinity purified, and monoclonal antibody purified; the products in the latter two groups are usually considered to be high-purity concentrates. Recombinant factor VIII concentrate is made in cell culture using recombinant technology.

*4.1.1. Intermediate-purity concentrates* (prepared solely by conventional precipitation techniques)

*4.1.2. AHF-HP (CSL).* This product is fractionated from cryoprecipitate. Contaminant fibrinogen and fibronectin are removed by precipitation with heparin. Factor VIII is precipitated with glycine/sodium chloride and lyophilised. Dry superheating is then applied at 80 °C for 72 h.

*4.1.3. Biostate (CSL).* Compared with AHF-HP, the method of manufacture of Biostate includes an additional gel filtration step designed to remove other proteins, particularly fibrinogen. The specific activity is 50 IU/mg prior to the addition of albumin which is consistent with that obtained in other high purity products prepared by conventional chromatography techniques. Viral inactivation is by both solvent-detergent inactivation and heat treatment at 80 °C for 72 hours.

4.1.4. *Haemate P (Centeon)*. The source cryoprecipitate undergoes adsorption with aluminium hydroxide followed by glycine sodium chloride precipitation. The resultant precipitate is pasteurised at 60°C for 10 h in the presence of stabilisers prior to a second sodium chloride precipitation. Albumin is added before lyophilisation.

## 4.2. **Recombinant factor VIII concentrates**

4.2.1. *Kogenate (Bayer) and Helixate (Centeon)*. The gene for factor VIII has been inserted into a cell line from baby hamster kidney (BHK). The secreted recombinant FVIII is processed by multiple purification steps, including two ion-exchange chromatography gel filtration/size exclusion chromatography and double immunoaffinity chromatography using a murine monoclonal antibody. The purified recombinant FVIII is then stabilised by the addition of pasteurised human albumin.

4.2.2. *Recombinate (Baxter) and Bioclata (Centeon)*. The genes for FVIII and vWF have been inserted into Chinese hamster ovary (CHO) cells. The vWF acts as a stabiliser for FVIII in cell culture. The recombinant FVIII produced is purified by single immunoaffinity chromatography using a murine monoclonal antibody. There are two subsequent ion exchange chromatography steps to complete the purification process. The purified recombinant FVIII is then stabilised by the addition of pasteurised human albumin.

4.2.3. *ReFacto (Wyeth Genetics Institute)*. The gene for B-domain deleted FVIII has been inserted into an established cell line from Chinese hamster ovary cells. The purification of the B-domain deleted recombinant FVIII involves five chromatographic steps and one virus inactivation step by solvent detergent. Stabilisation of the final product is without the addition of albumin. ReFacto contains trace amounts of hamster protein and murine protein.

4.2.4 *Animal protein and human albumin in recombinant FVIII*. Kogenate and Helixate contain trace hamster protein, trace murine immunoglobulin and human albumin as a stabiliser but no vWF. Recombinate and Bioclata contain trace amounts of hamster, bovine and mouse protein, human albumin as stabiliser and a trace of human vWF.

## 4.3. **Von Willebrand factor concentrates**

The following concentrates contain varying amounts of vWF: *CSL AHF and Biostate, Haemate P. Alpha VIII* and *Alphanate* also contain vWF and are under clinical trial in vWD.

## 4.4. **Prothrombin complex concentrates (PCCS)**

4.4.1. *Prothrombinex-HT (CSL)*. This concentrate, containing factors II, IX and X, is prepared from cryoprecipitate supernatant and is purified by DEAE ion exchange chromatography. After lyophilisation it is heated at 80°C for 72 h. Its use in haemophilia B is now largely replaced by MonoFIX (see 4.6.1.). It is registered for use in overdose of oral anticoagulants and in vitamin K deficiency.

#### **4.5. Concentrates for treatment of inhibitor patients**

4.5.1. *FEIBA (factor eight inhibitor bypassing activity) (Immuno)*. This activated prothrombin complex concentrate is prepared from cryoprecipitate supernatant which then undergoes controlled generation of FEIBA. After a series of purifying adsorption and filtration steps the product is vapour heated for 10 h at 60°C followed by 1 h at 80°C and lyophilised.

4.5.2. *Hyate C - porcine factor VIII (Speywood)*. Cryoprecipitate is prepared from porcine plasma and the factor VIII purified by affinity chromatography using polyelectrolyte resin. The final product is lyophilised. No additional stabilising proteins are added.

4.5.3. *NovoSeven recombinant factor VIIa (Novo Nordisk)*. Factor VII is produced as a single-chain glycoprotein (406 amino acids, 50 kDa), in a genetically transformed BHK cell line. Purification is by ion exchange and immunoaffinity chromatography, using murine monoclonal antibodies. During purification recombinant FVII is converted to the two-chain activated form. The recombinant VIIa is formulated as a freeze dried preparation. The recombinant VIIa contains non-coagulation factor contaminants as a result of the manufacturing process. These include trace amounts of hamster proteins from cells used in the fermentation process; bovine IgG and other bovine proteins from the bovine serum in the fermentation medium; and mouse IgG from the anti-FVII monoclonal antibody used in purification.

#### **4.6. Purified Factor IX concentrates**

4.6.1. *MonoFIX-VF (CSL)*. MonoFIX-VF is a chromatographically purified factor IX concentrate. The manufacturing process incorporates two viral inactivation or removal steps, solvent detergent and nanofiltration. Heparin and human AT III are added prior to the final formulation.

#### **4.7. Recombinant factor IX concentrate**

4.7.1. *BeneFIX (Wyeth Genetics Institute)*. The gene for FIX has been inserted into a cell line from Chinese hamster ovary. The recombinant FIX is produced in cell culture medium that is stabilised without human albumin. The recombinant FIX produced is purified via four chromatography steps and three (nanofiltration, ultrafiltration and diafiltration) membrane based filtration steps. The process does not employ the use of immunoaffinity chromatography using murine monoclonal antibody. The purified recombinant FIX is stabilised without the addition of human albumin.

#### **4.8. Coagulation factor concentrates for less common disorders**

##### **4.8.1. Fibrinogen concentrates**

4.8.1.1. *Fibrinogen (Immuno)*. Fibrinogen is prepared from cryoprecipitate supernatant after treatment with DEAE sephadex. Vapour heating is used to virally inactivate the product.

4.8.1.2. *Haemocomplettan P (Centeon)*. The fibrinogen is prepared from the glycine supernatant of the intermediate-purity FVIII process. The final product is a purified concentrate of fibrinogen pasteurised at 60°C for 10 h.

4.8.2. *Fibrin sealants*. Fibrin sealants are widely used in the local control of bleeding and may be used in patients with inhibitors. At present there are no locally produced sterilised fibrinogen concentrates or human thrombin solutions. Virally screened cryoprecipitate may be used as a source of fibrinogen.

#### 4.8.3. *Other concentrates*

4.8.3.1. *Factor VII (Immuno)*. Factor VII (Immuno) is a high purity concentrate. The manufacturing procedure includes a two step vapour heat inactivation at 60°C for 10 hours, followed by 80°C for 1 hour. Both steps are carried out under excess barometric pressure. The plasma procurement program provides for non-returning donor exclusion and a three month inventory hold on each plasma donation with look-back procedure. A PCR test for virus genome sequences of HIV, NBV and HCV is carried out on all batches.

4.8.3.2. *Factor VII (BPL)*. Factor VII is a highly purified concentrate. The manufacturing process includes purification of factor VII with a dedicated viral inactivation procedure. This concentrate is manufactured from plasma sourced from FDA approved sites in the USA.

4.8.3.3 *Factor XI (BPL)*. Factor XI is a highly purified concentrate. The manufacturing process includes purification of factor XI with a dedicated viral inactivation procedure. This concentrate is manufactured from plasma sourced from FDA approved sites in the USA.

4.8.3.4 *Factor XIII (BPL)*. Factor XIII is a highly purified concentrate. The manufacturing process includes purification of factor XIII with a dedicated viral inactivation procedure. This concentrate is manufactured from plasma sourced from FDA approved sites in the USA.

4.8.3.5. *Fibrogammin P (Centeon)*. This FXIII concentrate is prepared from cryosupernatant which is then further purified by ion-exchange chromatography prior to pasteurisation at 60°C for 10 h. Albumin is added as a stabiliser.

## 5. **Safety data on which recommendations are based**

### 5.1. ***Transfusion transmitted viral infection***

Several factors have contributed to the improved viral safety of modern plasma-derived coagulation factor concentrates. These include donor self-exclusion and screening policies, viral testing of plasma pools and specific virucidal procedures included in the majority of concentrate manufacturing processes. Currently individual human plasma donations are tested for anti-HIV 1 and 2, anti-HCV and HBsAg and some manufacturers are already PCR testing final product.

Reports of possible transmission of viral infection associated with the use of coagulation factor concentrates must be carefully scrutinised since infection may be acquired by other routes. Data from carefully conducted, prospective previous untreated patient (PUP)

studies provide substantial evidence of safety [6]. Systematic post-licensing pharmacosurveillance provides further evidence of viral safety.

*5.1.1. HIV (1 & 2) infection.* HIV transmission has not been reported by concentrates treated by dry heat treatment at 80°C for 72 h, pasteurisation at 60°C for 10 h, solvent/detergent or vapour heating. Current methods are therefore effective in preventing HIV and, barring failure of manufacturing processes, the risk of infection is very small [7-13].

*5.1.2. Hepatitis.* The risk of hepatitis has been markedly reduced but not eliminated. Concentrates subjected to dry heating at 80°C for 72 h appear to carry a very low risk of transmission of hepatitis [7, 8]. Solvent/detergent-treated coagulation factor concentrates also have an excellent safety record for hepatitis B and C in several PUP studies but their use has been linked with outbreaks of hepatitis A [11, 12, 14, 15]. PUP studies of viral safety of pasteurised products indicate a very low risk of hepatitis infection. At least seven cases of hepatitis B or C have been reported in patients who have received virally inactivated factor concentrates [9, 10, 16-19].

*5.1.3. Parvovirus B19.* Heat treatment, pasteurisation and solvent/detergent methods of sterilisation have been largely ineffective in preventing transmission of parvovirus B19 [20, 21]. Nanofiltration is thought to be effective in the removal of parvovirus. It may sometimes cause hypoplastic anaemia and severe systemic illness even in those with apparent normal immunity. Maternal infection can lead to hydrops fetalis and miscarriage. The resistance of parvovirus to currently used virucidal processes raises concerns over the failure of these methods to inactivate other, as yet unidentified, agents [22, 23].

*5.1.4. Cross-species infection.* Theoretical concerns exist over the possibility of transmission of infection by viruses, or other agents, from mammalian cell cultures or other processes using animal proteins. There are, however, no data to support this.

Porcine FVIII produced from porcine plasma also carries the theoretical risk of infection. The pigs used in the manufacture of this product are screened for several known porcine viruses but the concentrate is not subjected to specific virucidal treatment.

*5.1.5. Creutzfeld-Jakob disease (CJD).* The theoretical possibility of CJD transmission by transfusion has been extensively examined. There is no evidence that the causative agent is transmitted by plasma products. There have been no links between CJD and haemophilia [24].

## **5.2. Immune function**

Abnormalities of immune function in patients with haemophilia, occurring independently, of HIV, have been associated with the use of intermediate and low-purity clotting factor concentrates [25]. These include decreased CD4 and increased CD8 cell numbers, decreased IL2 secretion, cutaneous anergy and various defects of monocyte function. The reported immune changes may be due to non-HIV viruses or chronic liver disease.

The CD4 count in HIV-infected patients has been shown to stabilise (or decline more slowly) in patients treated with high-purity or recombinant factor VIII concentrate whilst

declining significantly in patients treated with intermediate-purity products [26-28]. No difference, however, in CD4 levels has been noted when patients on monoclonally or ion exchange prepared concentrates have been compared [29]. A survival advantage for the change to high-purity factor VIII concentrate has not been demonstrated [30, 31].

### **5.3. Inhibitors**

Retrospective studies have shown a prevalence of factor VIII inhibitors of 6-20%. A higher incidence (25-28%) has been observed in recent prospective studies of inhibitor development amongst PUPs treated with high-purity or recombinant FVIII [32, 33]. Two prospective studies of inhibitor formation in patients treated with intermediate-purity factor VIII concentrate have shown a similar cumulative incidence of inhibitor formation to that observed with high-purity or recombinant FVIII concentrates [34, 35], suggesting that the use of high-purity, or recombinant FVIII concentrate does not confer an increased risk of inhibitor formation.

Neoantigens may form during viral inactivation processing causing inhibitors to arise in previously untreated patients [36, 37]. This problem was associated with concentrates no longer manufactured, but surveillance is advised following the change of product.

The diagnosis and management of inhibitors is beyond the scope of this report, and is the subject of separate recommendations.

### **5.4. Thrombosis, myocardial infarction and DIC**

**5.4.1. Prothrombin complex concentrates.** Thromboembolism, disseminated intravascular coagulation and myocardial infarction have been associated with the use of prothrombin complex concentrates [38]. These complications are believed to be caused by activated coagulation factors. The risk is dose related, and may be increased by surgery or major bleeding. Thrombotic problems occur most commonly in patients with underlying cardiovascular disease and those who are immobile for long periods. Patients with pre-existing liver disease and premature infants seem particularly susceptible to develop DIC when treated with PCCs.

High-purity factor IX concentrates contain only trace amounts of other clotting factors. These products have no observable tendency to cause a clinically significant prothrombotic state and there is no evidence that activation of the coagulation system or thrombosis is associated with their use [39, 40].

**5.4.2. Factor XI concentrate.** Use of factor XI concentrates, particularly in high doses, has been associated with thrombosis [41]. Recent experiments have shown that doses 2-4 times greater than those recommended showed a thrombotic effect in the Wessler venous stasis model equivalent to that found with intermediate-purity factor IX concentrates. Elderly patients and those with a previous history of thrombosis or ischaemic heart disease are particularly at risk [42].

## **6. Therapeutic guidelines**

### **6.1. General recommendations**

**6.1.1. Patient information and consent.** Good practice dictates that the necessity for

treatment is appropriately explained to the patient and/or parent. This should include the advantages and risks of different therapies to allow an informed decision to be made. When consent has been obtained this should be recorded in the case notes.

*6.1.2. Vaccination against hepatitis A and B.* All patients who are not immune to hepatitis A or B and who currently receive, or may require, blood products should be vaccinated. At present revaccination with hepatitis A vaccine is not recommended and the vaccine is not currently licensed for use in children under the age of 1 year. Immunity to hepatitis B requires periodic reassessment and revaccination when appropriate.

*6.1.3. Risk reduction.* The use of fractionated, virucidally treated, concentrates when available has been the treatment of choice in achieving haemostasis in congenital coagulation factor deficiency since these products carry a lower risk of transmitting serious viral infection than cryoprecipitate or FFP [43] (*Grade B recommendation based on level III evidence*). It is acknowledged that despite new viral inactivation techniques it is possible that coagulation factor concentrates still transmit virus infection (see 5.1.). For this reason recombinant factor VIII is now preferred to treatment with plasma-derived concentrates.

*6.1.4. Use of DDAVP (desamino-8-D-arginine vasopressin, desmopressin).* DDAVP should be considered for all patients with mild/moderate haemophilia A or mild vWD, as this avoids the risk of viral transmission and is less expensive [44] (*Grade B recommendation based on level IIa evidence*).

DDAVP is generally administered intravenously at a dose of 0.3 mcg/kg diluted in 50 mL of 0.9% saline and infused over at least 30 minutes. An unlicensed intranasal spray preparation of DDAVP (Octim Nasal Spray, Ferring) is available at a dose of 300 mcg for adults and 150 mcg for children. An unlicensed concentrated subcutaneous preparation (Octim injection, Ferring) is also available and should be given at the usual dose of 0.3 mcg/kg. Efficacy should be demonstrated irrespective of the route employed, by measuring FVIII/vWF. Intranasal DDAVP has been shown to be comparable to the effect of an intravenous dose of 0.2 mcg/kg DDAVP [45].

DDAVP should be used with caution in elderly individuals, pregnant women and avoided in those with evidence of arteriovascular disease. Precautions to prevent fluid overload leading to hyponatraemia must be taken particularly in young children and DDAVP is probably best avoided in those younger than 2 years of age.

*6.1.5. Tranexamic acid.* Tranexamic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin and is available in an intravenous or oral preparation (both in suspension and tablet form). The intravenous preparation is not currently licensed in Australia. Tranexamic acid is particularly useful for bleeding from the gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP [46, 47] (*Grade A recommendation based on level Ia evidence*).

The recommended intravenous dose is 10 mg/kg 2-3 times daily and the oral dose 25 mg/kg 2-3 times daily [48] (*Grade B recommendation based on level IIa evidence*). Tranexamic acid is contra-indicated in patients with thromboembolic disease and should be avoided in patients with haematuria. It should not be used with FEIBA or other prothrombin complex concentrates (*Grade C recommendation based on level IV*

evidence). Tranexamic acid can be used in combination with NovoSeven.

**6.1.6 Aminocaproic acid.** Aminocaproic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin and is available as an intravenous preparation. It is particularly useful for bleeding from the gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP [47] (*Grade A recommendation based on level Ia evidence*).

The recommended intravenous dose is 1g hourly by continuous infusion. Aminocaproic acid is contra-indicated in patients with thromboembolic disease and should be avoided in patients with haematuria. It should not be used with FEIBA or other prothrombin complex concentrates (*Grade C recommendation based on level IV evidence*). Aminocaproic acid can be used in combination with NovoSeven.

## **6.2. Specific recommendations**

Licensed coagulation factor concentrates should be used in preference to unlicensed products. Each patient should be considered individually taking into account the following recommendations.

**6.2.1. Haemophilia A - factor VIII deficiency.** For patients for whom coagulation factor concentrate is the treatment of choice the following therapeutic strategies are recommended.

Recombinant factor VIII is the treatment of choice for all patients. As the introduction of recombinant factor VIII has to be prioritised then those who may benefit most should receive it first.

**6.2.2. von Willebrand disease.** DDAVP should be used for DDAVP-responsive vWD patients in preference to plasma-derived products. Where DDAVP is not likely to be effective, or is contra-indicated, FVIII concentrate or purified von Willebrand factor is the treatment of choice [49]. Cryoprecipitate is not virally inactivated and carries a risk of virus transmission. It is, however, recognised that there are some circumstances in which its use may be justified (*Grade B recommendation based on level IIb evidence*).

**6.2.3. Haemophilia B - factor IX deficiency.** Patients with factor IX deficiency should be treated with high-purity FIX concentrates because they cause less haemostatic activation than PCCs [39, 40] (*Grade A recommendation based on level Ib evidence*).

**6.2.4. Factor XI deficiency.** The majority of patients with FXI:C levels < 15 u/dL will suffer excessive bleeding following trauma or surgery and should be managed with infusions of factor XI concentrate [41]. In those with partial deficiency of factor XI (15-70 u/dL) bleeding is more difficult to predict. Where there is a clear history of abnormal bleeding and haemostatic support is required, the use of FXI concentrate is justified. The dose of FXI should be sufficient to raise the level of factor XI: C to 70 u/dL and the level should not

exceed 100 u/dL because of the risk of thrombosis (maximum dose 30 u/kg) [42, 50] (*Grade C recommendation based on level IV evidence*). Where there is no history of bleeding, tranexamic acid may be used alone, but in the event of subsequent excessive bleeding must be replaced by FXI concentrate. Patients should be assessed for preexisting risk of thrombosis and the concentrate should be used with great caution in those with a history of cardiovascular disease (*Grade C recommendation based on level IV evidence*). FFP might be a suitable alternative when FXI concentrate is contraindicated.

**6.2.5. Factor VII deficiency.** A purified, heat-treated FVII concentrate is available. This should replace PCCs and FFP as the treatment of choice in situations in which haemostatic support is necessary. The dose of FVII required depends on the severity of the deficiency and on clinical circumstances. The level of FVII required for haemostasis may be as low as 10-20 u/dL and this can be achieved by administering 5-10 i.u. FVII/kg (*Grade C recommendation based on level IV evidence*). *Recombinant factor VIIa can also be used in factor VII deficiency.*

**6.2.6. Factor II or X deficiency.** There is currently no specific factor II or X concentrate available and PCCs (see section 4.4.) remain the treatment of choice (*Grade C recommendation based on level IV evidence*).

**6.2.7. Factor V deficiency.** There are no specific concentrates available for use in FV deficiency and therefore FFP is the only available treatment (*Grade C recommendation based on level IV evidence*).

**6.2.8. Factor XIII deficiency.** FXIII concentrate prepared from human plasma is now available and is the treatment of choice (*Grade C recommendation based on level IV evidence*).

**6.2.9. Fibrinogen deficiency.** Unlicensed concentrates of fibrinogen have recently become available and since these products are virally inactivated it is anticipated that they may replace cryoprecipitate in the near future (*Grade C recommendation based on level IV evidence*).

**6.2.10. Future treatment of hereditary coagulation disorders.** Recombinant factor VIII and IX will be used widely because of continuing concerns about the safety of plasma-derived concentrates. It is anticipated that recombinant factor VIII, which is formulated without addition of human albumin as a stabiliser, will become licensed. Furthermore it is known that recombinant factor VIII being manufactured without using any bovine or human proteins will eventually replace current products. Recombinant factor IX is currently licensed in the USA. It should be introduced for routine haemophilia B care using criteria similar to those for recombinant factor VIII.

## **7. Clinical audit**

The regular assessment of therapeutic practice by audit is an essential component of good

haemophilia practice. Adherence to these guidelines may be audited in many ways, for example:

- 1 Are patients receiving the appropriate recommended product?
- 2 Are there appropriate pharmacosurveillance arrangements in place, e.g. viral infection and inhibitor formation?
- 3 Are there clear local arrangements to ensure that patients receive the appropriate treatment?
- 4 When a non-licensed product is used are data collected which can be used to help with its evaluation?
- 5 Is there a system for recording adverse reactions and are these appropriately reported nationally?

## **8. Distribution of guidelines**

These guidelines have been distributed to the following:

Royal College of Pathologists of Australasia  
Royal Australasian College of Surgeons  
Royal Australasian College of Physicians  
Royal Australian and New Zealand College of Obstetricians & Gynaecologists  
Royal Australian College of Ophthalmologists  
Royal Australian College of General Practitioners  
Australian College of Pharmacy Practice  
Australian College of Emergency Medicine  
Royal Australasian College of Dental Surgeons  
Australian and New Zealand College of Anaesthetists  
Australasian Society of Blood Transfusion  
Haematology Society of Australia  
All Health Ministers

## **9. Declaration by members of the Haemophilia Foundation Australia Medical Advisory Panel**

MAP members have signed a Conflict of Interest statement declaring any pecuniary interest in product manufacturing companies.

J V Lloyd

*Chairman*

*Haemophilia Foundation Australia Medical Advisory Panel*

*March 2000*

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## Appendix 1

### *Levels of evidence*

<u>Level</u>	<u>Type of evidence (based on AHCPR 1992)[5]</u>
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparison studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

### *Grading of recommendation*

<u>Grade</u>	<u>Recommendation (based on AHCPR)</u>
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality