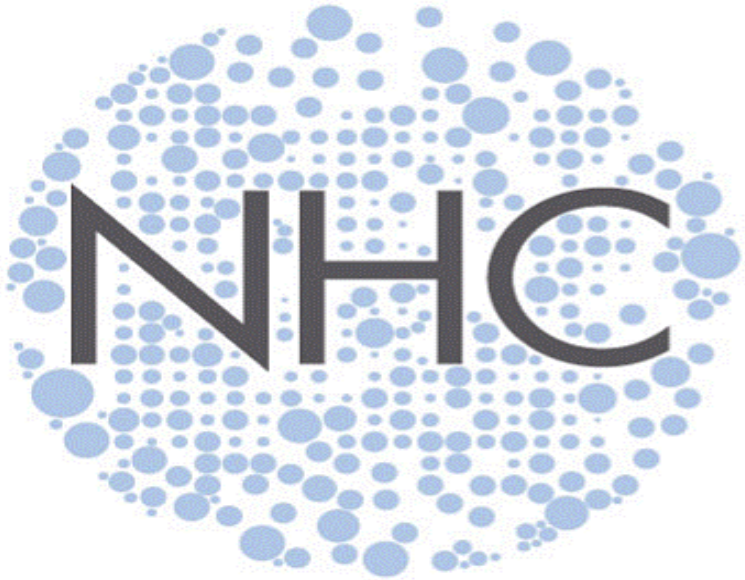

National Haemophilia Council

Acute Treatment Guidance for Adults with Haemophilia and Related Bleeding Disorders

Adult Haemophilia Treatment Centres (CCC) Ireland:	
The National Coagulation Centre (NCC),St. James's Hospital, Dublin 8	**Ph: (01) 4162141**
Cork Coagulation Centre, Cork University Hospital, Wilton,Cork City	**Ph: (021) 4922278**
Haemophilia Treatment Centre, Galway University Hospital, Newcastle Road,Galway.	**Ph: (091) 524222**

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Current version	**Version 4**	

		Document Change Log
Version 2	**Layout changes**	• Table of contents added. • Chapters reallocated to avoid repetition. • Dosage formulas changed to body of text rather that appendix. • Management of Inhibitors detailed in FVIII and FIX. • Hemlibra added as treatment for patients with Factor VIII deficiency and inhibitors • The addition of a new chapter on the management and treatment of Bleed Disorders of Unknown Aetiology.
	Product Changes	• CFCs product change: Advate to Elocta • CFCs product change: Benefix to Alprolix
Version 3	**Product changes**	• Factor VIII replacement products added as a treatment of trauma induced or spontaneous bleeding, or if an invasive procedure with a major risk of bleeding is needed. • Alprolix administration guidance • Veyvondi as a treatment for VWD • Coagadex as a treatment for Factor X • Octaplex as a treatment for Factor II • Volumes added to Quick Reference, Appendix 2.
	Layout changes	• National Advisory Immunisation Committee (NIAC, 2023) anaphylaxis algorithm added. • Appendix 3 Quick Reference- Emergency treatment of patients with bleeding disorders added.
Version 4	**Product changes**	• Altuvoct as a treatment of Factor VIII • Fibryga as a treatment for fibrinogen deficiencies • Octim (Subcutaneous desmopressin) added • Laboratory tests for the measurement of Factor VIII products added
	Layout changes	• Quick reference guide on information for healthcare providers added to the start of the document. • Section numbering taken out and table of contents updated to include level 1 headings only. • Appendix 3 Quick Reference- Emergency treatment of patients with bleeding disorders removed and replaced with quick reference guide on page 5 and 6.

Table of contents

Quick Reference Guide - 1 - Urgent care for adults (>/=16 years) with inherited or acquired bleeding disorders – Practical information for Healthcare Professionals

Actions when managing an adult (>/=16 years) with an inherited or acquired Bleeding Disorder who presents acutely.

1. Ask the person for their Bleeding Disorder Registration Card
2. If they don't have their Registration card, ask for details;
    a. Diagnosis
    b. Baseline level (if known and applicable)
    c. Treatment of choice (e.g., clotting factor concentrate, desmopressin, Tranexamic acid, platelet transfusion)


Bleeding Disorder ID Card
Test PATIENT
01-01-1980 MRN: 00000012
Diagnosis
Severe hereditary factor VIII deficiency disease without inhibitor (disorder)
Low von Willebrand factor

3. Call their main Bleeding Disorder Treatment centre as soon as possible. There is 24/7 cover and the direct contact details are:

NCC Treatment Centre Working hours, Mon-Fri, 0830-1700 hrs 01 416 2141 Email – NCC@STJAMES.IE Out of hours and Bank holidays – 01 410 3132 Alternatively, phone (01) 410 3000 and ask for the Haematology SHO on call.	**CUH Treatment Centre** Working hours, Mon-Fri, 0830-1700 hrs 021 4922278 or 0879683246 After 5pm & bank holidays - 021 4546400 and ask for Haematology Registrar On Call
CHI Treatment Centre (<16years only) Working hours, Mon-Fri, 0830-1700 hrs Haemophilia Nurse Direct Line - 01 4096939/40 Pager 01 4096100 Bleep 8732/8733 After 5pm or at weekend/bank holidays, phone the hospital and ask to speak to the Haematology Registrar on call	**GUH Treatment Centre** Mon – Fri, 0800 - 1600 hrs. Direct line 091 542348 or Hospital No: 091 524222 and ask for Bleep 673 After 4pm or at weekend/bank holidays - Hospital No as above and ask for doctor 'on call' for Haematology.

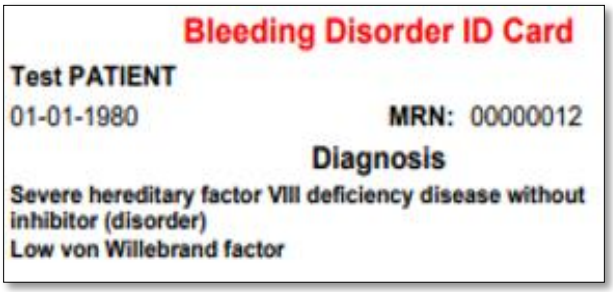
4. ***If there is any delay in getting through to the Treatment centre, contact the Coagulation Consultant on call via switchboard at the relevant treatment centre hospital.***

5. Ensure that the local Haematology service and Blood Transfusion and Haematology laboratories are aware that a person with a bleeding disorder diagnosis has presented for care.

6. If a person with a bleeding disorder presents with bleeding:
    a. Activate the standard resuscitation measures.
    b. Give Tranexamic acid 1 g IV stat (unless oral dose taken within last 8 hours).
    c. Contact the person's treatment centre urgently.

*Quick Reference Guide – 2 - Actions when managing a person with an adult (>/= 16 years) with an inherited or acquired Bleeding Disorder who presents for **an unplanned procedure***

1. Ask the person for their Bleeding Disorder Registration Card
2. If they don't have their Registration Card, ask for details;
    a. Diagnosis
    b. Baseline level (if known and applicable)
    c. Treatment of choice (e.g., clotting factor concentrate, desmopressin, Tranexamic acid, platelet transfusion)



3. Request a haemostatic treatment plan from the person's Bleeding Disorder Treatment centre.

    For the NCC, this form can be accessed from the tab **Patient having a procedure at** https://www.stjames.ie/services/hope/nationalcoagulationcentre/

    For other centres, please contact them with the following information:
    a. Details of the planned procedure – precise information is required.
    An assessment of bleeding risk would be helpful.
    b. Date of planned procedure
    c. Operator/Surgeon/Endoscopist name
    d. Hospital and location (e.g., day surgery, endoscopy)
    e. Contact person and contact details (if possible, for co-ordination)

4. Ensure that the local Haematology service and Blood Transfusion and Haematology laboratories are aware that a person with a bleeding disorder diagnosis has a planned procedure and copy them into all communications, paper and electronic.

5. If a person with a bleeding disorder presents with bleeding post procedure:
    a. Activate the standard resuscitation measures.
    b. Give Tranexamic acid 1 g IV stat (if not already taking this medication).
    c. Contact the person's treatment centre urgently.

Frequently Asked Questions

1. What should be done when a person reports that they have a bleeding disorder?

It is essential to contact the person's treatment centre as soon as you become aware that they have a bleeding disorder. Centres maybe experiencing high volume of calls, please continue to try and establish contact with the centre, including via the hospital switchboard if required.

Even if the person presents with symptoms unrelated to bleeding, management of other medical conditions may be different for a person with a bleeding disorder.

All treatment centres in Ireland have staff available on a 24/7 basis to give clinical advice on treating people with bleeding disorders. Please refer to the contact details in the **Quick Reference Guide 1.**

2. Treatment centres:

In Ireland, people with inherited or acquired bleeding disorders are registered at one of four specified treatment centres.

For adults (>/= 16 years)	For children(<16years)
• National Coagulation Centre at St James's Hospital, Dublin • Cork Coagulation Centre at Cork University Hospital • Galway University Hospital	• Paediatric Coagulation Centre, Children's Health Ireland at Crumlin • Cork Coagulation Centre at Cork University Hospital • Galway University Hospital

Relevant clinical information is available on the National Electronic Health Record (EHR) for Haemophilia and bleeding disorders called "indici" (access is available to treatment centre staff on a 24/7 basis).

3. What bleeding disorders are included?

Inherited bleeding disorders include Haemophilia, Von Willebrand disease, rare coagulation factor deficiencies, platelet function disorders and Bleeding Disorder of Unknown Cause (BDUC).

Acquired bleeding disorders include acquired haemophilia, acquired Von Willebrand Disease, other acquired factor deficiencies and platelet disorders

4. What information will a person have about their bleeding disorder?

People who have been diagnosed with a bleeding disorder are registered on the National EHR and are sent a registration card by their treatment centre which should be carried at all times. This card has the person's diagnosis and factor level (if applicable) on one side and the name and contact details of their treatment centre on the other side.

Some people will have access to their own bleeding disorder treatment records through a patient portal called "myindici". They will have access via an App on their phone.

Sometimes, a person will state their bleeding disorder diagnosis verbally, without having a registration card or other information to hand.

5. What other communications are needed about a person with a bleeding disorder?

Always contact your local Haematology service. The bleeding disorder treatment centres can give advice on haemostatic treatment but the local medical and Haematology teams are responsible for onsite care.

6. How do I Access Clotting Factor Concentrate?

If a person may need clotting factor concentrate, contact your local Blood Transfusion Laboratory (public hospitals with an emergency department have at least one dose of all commonly used types of clotting factor concentrate. For private hospitals, an emergency delivery of clotting factor concentrate may be needed or the person could be transferred to a public hospital for treatment in conjunction with the treating centre).

7. What if factor levels need to be measured?

The treatment centres can advise on how to arrange factor levels if these are needed, either in the local Haematology Laboratory or sent by the local laboratory to the specialist coagulation laboratories associated with the treatment centres.

8. What if a person with a bleeding disorder is scheduled for a non-urgent planned procedure?

In general, major surgeries will be done in one of the main treatment centre hospitals for people with severe bleeding disorders. However, people may undergo minor procedures in external hospitals and people with milder bleeding disorders often have surgeries outside the main treatment centre hospitals.

If you become aware that a person with a bleeding disorder is planned to have an invasive procedure, contact the treatment centre at least 2 weeks in advance for a detailed haemostatic treatment plan, including the haemostatic medications needed and whether these will be administered in the treatment centre or should be given locally, whether factor levels are required to be tested (if applicable) and what to do if excessive bleeding occurs.

For the NCC, the treatment plan form can be accessed from the tab **Patient having a procedure**
https://www.stjames.ie/services/hope/nationalcoagulationcentre/

For other centres, please contact them – please contact them by phone/email/post as appropriate.

Introduction

The National Haemophilia Council (NHC) was set up in response to the findings of the Lindsay Tribunal in 2001 and established as a statutory body in 2004 (S.I. No. 451 of 2004.) The principal function of the NHC is to provide advice, information, support and education on all aspects of haemophilia to the Health Minister, Health Service Agencies and Persons with or affected by haemophilia. Under this remit the Council works continuously to provide Clinicians with current and comprehensive guidance for the safe and effective management of persons with haemophilia and related bleeding disorders.

Haemophilia refers to inherited bleeding disorders caused by the absence or low level of specific proteins called clotting factors (specifically factor VIII or factor IX in the blood). Related bleeding disorders are caused by deficiencies in other clotting factors such as VWF or by abnormalities in blood platelets. The most common bleeding disorders are:

- Factor VIII Deficiency (Haemophilia A)
- Factor IX Deficiency (Haemophilia B)
- Von Willebrand Disease (VWD)
- Platelet Function Disorders (PFDs)
- Rare Bleeding Disorders (RBDs) i.e., Inherited deficiencies of Factors I, II, V, VII, X, XI, XIII
- Bleeding disorder of unknown cause (BDUC)

Due to the complexity of haemophilia and its treatment, care of persons with these bleeding disorders should be coordinated by a specialist centre known as a Comprehensive Care Centre (CCC).

The specialist multidisciplinary services and care that these centres provide have been shown to contribute significantly to improved outcomes and better quality of life for persons with bleeding disorders. The NHC recommends that all persons diagnosed with a bleeding disorder should be registered with and monitored by one of the designated CCCs in Ireland, which are:

- The National Coagulation Centre (NCC), St. James's Hospital, Dublin 8 – people aged >16 years
- Cork Coagulation Centre, Cork University Hospital – all age groups
- Paediatric CCC - Children's Health Ireland at Crumlin – people <16 years

However, the NHC recognises that on occasion, persons with haemophilia may present to a non-specialist service requiring treatment and/or intervention e.g., with a bleed. In these circumstances non-specialist clinicians are required to assess the patients and initiate management incollaboration with the patient's CCC. Accordingly, the NHC has commissioned the guidance to assist healthcare professionals in the immediate management of adult persons with haemophilia. The information is presented in condition-specific chapters in which the following information is included:

- General Information
- Disease Severity
- Bleed / Suspected Bleed Management

The management of the allergic reactions to CFCs, surgical management, the management of pregnancy including the management of labour and the management of the newborn, are all dealt with in separate chapters.

Key Statements

- Acute treatment of all persons with an inherited bleeding disorder should be coordinated by the CCC with which the patient is registered. This guidance should be used in the management of persons with bleeding disorders as an adjunct to advice received from the CCC.
- In the event a person with a diagnosis of haemophilia or related bleeding disorder presents to a hospital requiring assessment and/or treatment and/or intervention the treating Clinician should:
  - Contact the CCC (the patient should have a registration card detailing their diagnosis and CCC)
  - Confirm the bleeding disorder diagnosis, factor level and treatment of choice with the CCC
  - Agree a management and follow up plan with the CCC.
- Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g., Altuvoct or Elocta (according to designated treatment of choice) for FVIII deficiency and Alprolix for FIX deficiency.
- The Prescriber must note that not all patients with mild FVIII or FIX deficiency require clotting factor concentrate as the use of alternative treatments may be indicated e.g.,Desmopressin or Tranexamic Acid. The patient's treatment of choice must be confirmed with the relevant CCC.
- Persons under the age of 16 years (Children) should be treated in accordance with paediatric guidance.

Scope

The guidance applies to: Adults with Inherited Bleeding Disorders who require immediate treatment/intervention in non-specialist centres including the following;

- Factor VIII Deficiency (Haemophilia A)
- Factor IX Deficiency (Haemophilia B)
- Von Willebrands Disease
- Rare bleeding disorders (inherited deficiencies of factors I (Fibrinogen), II, V, VII, X, XI, XIII)
- Inherited disorders of Platelet function
- Bleeding disorder of unknown cause

Definitions/Glossary

Throughout this document the following abbreviations / acronyms are used:

BDUC	Bleeding Disorder of Unknown Cause
BPAs	Bypassing agents
CBA	Collagen binding assays
CCC	Comprehensive Care Centre
CFC	Clotting Factor Concentrates and other biological products
CUH	Cork University Hospital
CVAD	Central Venous Access Device
FBC	Full blood count
GP1bM	Glycoprotein 1b M activity
PICC	Peripherally Inserted Central Catheters
RCo	Ristocetin Cofactor Activity
SJH	St James's Hospital
SPC	Summary of Product characteristics
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor

Assessment of patient

Recommended assessment of the patient presenting with a bleeding episode

- Perform initial evaluation and assessment.
- Identify the site of the suspected bleed
- Assess for compression of vital structures e.g., airway, nerves or blood vessels, and manage accordingly.
- Undertake pain assessment and treat accordingly- e.g., SJH Pain Management Guidelines
- Where possible, obtain details from the patient or relative regarding the bleeding disorder diagnosis, factor level, inhibitor status and treatment of choice
- Check if the patient is carrying their bleeding disorder registration card
- Weigh the patient or estimate weight where necessary (Kilograms only)
- Confirm the date, time and dose of the last factor concentrate infusion received (especially important if the patient usually takes prophylaxis)
- Undertake initial blood testing to include: FBC, Biochemistry, Group and Cross-match, PT/APTT and Factor Levels – at least 6 mls blood in citrate sample bottles (note that levels do not need to be reported in order to treat a bleed as the dose can be calculated if the date of the last CFC treatment and the registered baseline factor level are known)
- Arrange appropriate imaging but **DO NOT DELAY** haemostatic treatment if a bleed is suspected. Treat first, image after.
- If in doubt manage as a bleed, but consider alternative diagnosis and investigate accordingly.

Communication to CCC and local Haematology service

- **Contact the patient's CCC IMMEDIATELY following the initial assessment**
- Confirm the patient's bleeding disorder diagnosis, factor level, inhibitor status and treatment of choice
- Agree a management plan and follow up with the CCC
- The local Haematology service should be made aware of the management plan agreed with the CCC, this is to allow the local team to give local advice and support to the patient and the healthcare team, and also to manage local treatment stock levels with the Blood Transfusion laboratory.

While this document aims to give guidance and direction to healthcare professionals the information in this document must be supplemented by the use of product SPCs which are available on the following website https://www.hpra.ie/

Factor VIII Deficiency (Haemophilia A)

General Information

Factor VIII deficiency (Haemophilia A) is a bleeding disorder caused by a deficiency of clotting factor VIII. This condition affects 1 in 5,000 male live births and is five times more common than Factor IX deficiency (Haemophilia B). Female carriers of Haemophilia A may have low FVIII levels and one third have levels similar to mild Haemophilia i.e., 5-40% (0.05-0.40 IU/ml). These affected females may also need treatment for bleeding, menorrhagia, prior to surgery or labour and delivery.

Severity

Severity relates to the baseline level of factor VIII.

Severity	Factor VIII Activity Level
Severe disease	<1% (<0.01 IU/ml)
Moderate disease	1–5% (0.01-0.05 IU/ml)
Mild disease	>5% (>0.05 IU/ml)

Table 1 Factor VIII Deficiency Severity Categories

Treatment Administration

- **Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g., Altuvoct or Elocta for FVIII deficiency**
- **There are currently two CFC products available for the treatment of Factor VIII deficiency so ensure you use the product name when prescribing and requesting the product for the patient**
- Altuvoct must not be used as a Factor VIII product for patients on Hemlibra.
- Currently the only Factor VIII product suitable for use in patients on Hemlibra is **ELOCTA**
- **The prescriber must note that not all patients with mild FVIII deficiency require clotting factor concentrate, and the use of alternative treatments may be indicated e.g., Desmopression and/or Tranexamic Acid**
- **The patient's treatment of choice must be confirmed with the relevant CCC.**

The Clinician should establish the treatment of choice i.e., Altuvoct, Elocta, Desmopressin Injection and/or Tranexamic Acid. Clotting Factor Concentrates for acute treatment are held in the Blood Transfusion department of each hospital.

Clotting Factor Concentrate – Elocta - Please refer to product SPC for the most up to date information, advice and cautions.

Altuvoct is the factor used in the treatment and prophylaxis of bleeding in patients with congenital factor VIII deficiency.

Elocta is the factor used in the treatment of bleeding episodes in patients with congenital factor VIII deficiency who also use a subcutaneous prophylactic medication called Hemlibra.

Both Altuvoct and Elocta comes as a powder and solvent in a pre-filled syringe that must be reconstituted for solution

Both are administered as a bolus infusion at a rate not exceeding 10mls per minute.

Dose Calculation- Altuvoct and Elocta

Bolus Dosing in FVIII Deficiency CFC i.e., Altuvoct and Elocta

Rise required = desired level of factor concentrate (%) minus baseline factor level (%)

Note: 100% = 1.0 IU/ml, 50% = 0.5 IU/ml, 5% = 0.05 IU/ml)

$$\textbf{Dose required} = \frac{\textbf{Rise required (\%) x Weight (kgs)}}{\textbf{K}}$$

K factor for FVIII = 2

$$\frac{\textbf{100\% (1.0 IU/ml) – 0 \% (<0.01 IU/ml) x 50kg = 2500 units}}{\textbf{2}}$$

Example: A 50kg patient with a FVIII: C* <0.01 IU/ml (<1%) who needs a post factor level of 1.0 IU/ml (100%) willrequire 2500 units FVIII concentrate. Round up to the nearest available vial size.

Bleeding Site	**Target initial post treatment FVIII Factor levels**
Major bleed	1.0 IU/ml (100%)
CNS or bleed involving peripheral nerve	1.0 IU/ml (100%)
Ileopsoas /retroperitoneal	1.0 IU/ml (100%)
Tongue/neck/retropharyngeal	1.0 IU/ml (100%)
Gastro-intestinal	1.0 IU/ml (100%)
Haemarthrosis	0.5 – 0.7 (50 - 70%) IU/ml
Minor bleed	0.5 IU/ml (50%)
Laceration requiring sutures	0.4 IU/ml (40%)
Haematuria	High fluid intake +/- rise to 0.3-0.5 IU/ml (30-50%)
Minor surgery (angiogram, lumbar puncture)	1.0 IU/ml (100%)
Liver biopsy or central venous catheter	1.0 IU/ml (100%)
Major surgery	1.0IU/ml (100%)

Table 2 Desired initial Post Treatment Factor Levels for Bleeds Types in Persons with FVIII deficiency

Pre filled glass syringes are not compatible with clave connectors, therefore if administering Altuvoct and Elocta via a clave connector, PICC line or CVAD the reconstituted solution should be drawn into a plastic syringe prior to administration.

Administration- Altuvoct and Elocta

- Altuvoct or Elocta should be administered as a slow intravenous push at a rate not exceeding 10 mls per minute.
- **A post treatment factor level should be drawn 20 minutes' post administration** (two coagulation samples send to local laboratory for forwarding to the CCC for analysis).
- Liaise with CCC regarding the post treatment level result in case further treatment is required.

Laboratory FVIII Assays for patients on Altuvoct and Elocta

Product Name	Factor VIII Assay Required
• Altuvoct	• Actin FSL Factor VIII (FVIII: Altuvoct)
• Elocta in combination with Hemlibra	• Chromogenic Factor VIII (FVIII:Chr)
• Elocta (non Hemlibra patient)	• One stage Factor VIII (FVIII:C)

Desmopressin

Please refer to product SPC for the most up to date information, advice and cautions.

Desmopressin solution for injection (Desmopressin Acetate) is a synthetic analogue of the natural hormone arginine vasopressin. It is indicated for use in managing bleeds in some persons with Factor VIII deficiency and Von Willebrand disease/Low VWF by increasing plasma levels of FVIII and VWF.

Dose Calculation- Desmopressin

Desmopressin can be administered intravenously or subcutaneously at a dose of 0.3 micrograms/kg.
The maximum total dose recommended for any patient is 27 micrograms.
There are two product forms available for Desmopressin; DDAVP (intravenous only) or Octim (subcutaneous or intravenous use)
Example: A 60kg patient requiring desmopressin, the dose should be calculated as 60 kg x 0.3 micrograms = 18 micrograms.

Dose Administration- Desmopressin

DDAVP only for intravenous use comes in 1ml ampoule which contains Desmopressin acetate **4 micrograms per ml** in asterile, aqueous solution for injection.
DDVAP should be added to 50mls of normal saline using an aseptic technique.
The 50ml solution should be administered intravenously over 20 minutes.

Example: A 60kg patient requiring DDAVP - The intravenous preparation has a concentration of 4 micrograms /ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 4.5mls of DDAVP in 50mls of normal saline and this will be administered IV over 20 minutes.

Octim is a desmopressin product suitable for subcutaneous injection and intravenous use and comes in a 1ml formulation at a concentration of 15 micrograms per ml

The subcutaneous preparation has a concentration of 15 micrograms/ml. Therefore, the subcutaneous dose for a 60kg patient (18 micrograms) would be prepared by drawing up 1.2 mls of Octim into a syringe and administered subcutaneously

Octim can also be administered intravenously. The intravenous preparation has a concentration of 15 micrograms per ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 1.2ml of Octim in 50mls of normal saline and this will be administered IV over 20 minutes.

Contraindications/Cautions- Desmopressin

Desmopressin is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in the SPC
- Habitual or psychogenic polydipsia
- A history of unstable angina and/or known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion (SIADH)
- Von Willebrands disease type II B where the administration of Desmopressin may result in pseudothrombocytopenia due to the release of clotting factors which cause platelet aggregation

Special warnings and precautions for use:

Fluid balance

- Desmopressin should only be administered under the supervision of a specialist with appropriatelaboratory facilities available for monitoring of the patient.
- It is recommended to maintain fluid and electrolyte balance. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatraemia with or without accompanying warning signs or symptoms. Local practice is to ensure no more than 1.5 litres total fluid intake in adults in 24 hours post Desmopressin infusion.
- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia Treatment with Desmopressin should be interrupted

or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis) as well as in excessive bleeding, and the fluid and electrolyte balance should be carefully monitored.

- Special attention should be given when Desmopressin is co-administered with other drugs affecting water and or sodium homeostasis. In patients with chronic therapy with drugs affecting water and/or sodium homeostasis, Desmopressin Injection should be administered after confirmation of normal baseline sodium.

- When repeated doses are used to control bleeding in haemophilia or von Willebrand disease, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or determining plasma sodium or osmolality.

Thrombotic Risk

- Due to post marketing reports, with Desmopressin injection, of deep vein thrombosis, cerebrovascular accident and disorder (Stroke), cerebral thrombosis, myocardial infarction, angina pectoris and chest pain, considerations should be taken before using Desmopressin injection in elderly patents and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice is not usually recommended for patients > 55years.

Other Conditions

- Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.
- The benefits of Desmopressin versus other haemostatic therapies should be carefully assessed in situations where prolonged haemostasis is required including active post-operative bleeding and variceal bleeding in patients with cirrhosis
- Continuous blood pressure monitoring is recommended during infusion of Desmopressin Injection
- Precautions must be taken in patients at risk for increased intra cranial pressure.
- Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50ml/min)

Tranexamic Acid (Cyklokapron)

Please refer to product SPC for the most up to date information, advice and cautions.

Tranexamic Acid is an anti-fibrinolytic agent, indicated in patients with haemophilia for short-term use (two to eight days), to reduce or prevent haemorrhage.

Tranexamic Acid is available in tablet and Intravenous Injection form.

Dose Calculation- Tranexamic Acid (Cyklokapron)

- **Oral** / Tablet form (500 mg Tranexamic Acid)

  Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- **Intravenous** Injection (500mg in 5ml ampoule)
  Recommended dose 10 mg/kg TDS

Dose administration- Tranexamic Acid (Cyklokapron)

Bolus injection – The required dose can be administered undiluted, very slowly i.e. at a rate of 100mg/min.
Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

Contraindications/Cautions- Tranexamic Acid (Cyklokapron)

Cyklokapron tablets are contraindicated in patients with:

- Severe renal impairment
- Subarachnoid haemorrhage
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Hypersensitivity to Tranexamic acid or any of the other ingredients.

Special warnings and precautions for use of Cyklokapron tablets:

- Reduction in dosage recommended in patients with renal insufficiency.
- Use with caution in patients with massive haematuria from the upper urinary tract.
- Use with caution when intravascular coagulation is in progress.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use Cyklokapron tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use Cyklokapron Tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.

Cyklokapron solution for injection or infusion is contraindicated in patients with:

- Hypersensitivity to Tranexamic Acid or any of the other ingredients.
- Acute venous or arterial thrombosis

- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding
- Severe renal impairment
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)
- Tranexamic Acid should not be administered by the intramuscular route

Special warnings and precautions for use of Cyklokapron solution for injection or infusion:

- Convulsions
- Visual Disturbances
- Haematuria
- Thromboembolic events
- Administer with care in patients receiving oral contraceptives because of increased risk of thrombosis
- Disseminated intravascular coagulation.

Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis).

Patients with Factor VIII deficiency and inhibitors

- Inhibitors (antibodies against infused FVIII concentrate) are a common occurrence in FVIII deficiency (Haemophilia A).
- The incidence of inhibitor development is approximately 30% and a FVIII inhibitor may be present at low levels ("low responding", inhibitor titre <5 Bethesda Units (BU)) or high levels ("high responding", inhibitor titre ≥ 5BU).
- Not all inhibitors are persistent, as low responding inhibitors may wane with continued regular factor infusions or high responding inhibitors may be cleared with immune tolerance therapy.
- A small number of patients have persistent, high responding inhibitors and these patients cannot receive FVIII concentrate to treat or prevent bleeding but should receive alternative treatments such as bypassing agents or Hemlibra (see below).
- Patients with FVIII deficiency have a life-long risk of developing an inhibitor although the majority of inhibitors occur before the first 50 (and often before the first 20) exposure days.
- Patients with mild FVIII deficiency, who only require FVIII concentrate intermittently, may be well into adulthood before reaching 20 exposure days.
- It is important to identify patients with FVIII deficiency that have a current or past history of inhibitors.

In all cases where there is a history of an inhibitor, it is crucial to contact the patient's CCC to confirm the patient's optimal treatment regimen.

Critical information that is required to be obtained is listed below and can be confirmed with the patient or on the patient's registration card from their Comprehensive Care Centre (CCC).

Important information on patients with a history of FVIII inhibitors
Is inhibitor present currently or in past history?
What is patient's current treatment of choice?
Has patient ever received Immune tolerance treatment? If yes, when was this given and did the patient achieve eradication of the inhibitor?

Table 3 Important information on patients with a history of FVIII inhibitors

Treatment Options for Factor VIII patients with inhibitors

Bypassing agents for Factor VIII patients with inhibitors

Bypassing agents (BPA) are clotting factor concentrates designed to "bypass" the need for FVIII and are given when the patient's inhibitor titre means that FVIII concentrates will not be effective(high responding inhibitors) or when the past history of inhibitors was so severe that further exposure to FVIII is contra-indicated, (An example of this is where a patient with mild FVIII deficiency develops an inhibitor which cross-reacts with their endogenous FVIII and this results in the development of severe FVIII deficiency).

Please refer to product SPC for the most up to date information, advice and cautions.

There are two bypassing agents available in Ireland:

- **Feiba** – an activated prothrombin complex concentrate (aPCC) containing factors II, VII, IX and X. The clotting factors are present in their inactive (zymogen) form and also in an activated form, as activation occurs as part of the manufacturing process. Feiba is derived from human blood donations and the product is dual virally inactivated.
- **NovoSeven** – recombinant activated factor VII (rFVIIa) can activate Factor X on the surface of activated platelets and thus, overcome the absence of FVIII. The dose of activated factor VII is supra-physiological (about 10 times the normal level of FVII in the blood).

  NovoSeven is a fully recombinant clotting factor and does not contain human derived material.

Cautions with Bypassing Agents, in patients with Factor VIII inhibitors

- Arterial and venous thrombotic complications have been reported during and after treatment with BPAs.

- Be aware of other risk factors for thrombosis in patients receiving BPAs and mitigate these where possible e.g., use of mechanical thromboprophylaxis if appropriate, avoidance of smoking, maintain ideal body weight, minimise periods of immobility.
- Use BPAs at the lowest effective dose and for the shortest duration possible when treating acute bleeding or managing invasive procedures.
- Avoid concomitant antifibrinolytic drugs e.g., Tranexamic acid unless advised by CCC (See also advice on dosing below).

Dose Calculation of Bypassing Agents, in patients with Factor VIII inhibitors

Please refer to product SPC for the most up to date information, advice and cautions.

BPA	Initial dose	Subsequent dose and frequency	Important Notes
Feiba	50-80 units/kg	50 units/kg every 8-12 hours	DO NOTEXCEED a total dose of 200 units/kgin a 24-hour period
NovoSeven	90 micrograms/kg	90 micrograms/kg every 2-4 hours	

Table 4 Dose Calculation of Bypassing agents, in patients with Factor VIII inhibitors

Prophylaxis in FVIII deficient patients with inhibitors

BPAs may be used for prophylaxis as documented below:

- Feiba 50-80 units/kg IV three times per week
- NovoSeven 90 micrograms/kg three times per week or more frequently if required (may be given daily)

Hemlibra- FVIII mimetic for prophylaxis

Please refer to product SPC for the most up to date information, advice and cautions.

- Hemlibra is a bispecific antibody which acts to co-locate FIXa and FX on the surface of activated platelets and so mimics the role of FVIII as a co-factor in coagulation.
- It is administered subcutaneously and may be given once a week, once a fortnight or once every 4 weeks.
- The purpose of Hemlibra is to prevent spontaneous bleeding – IT DOES NOT NORMALISE HAEMOSTASIS. Therefore, haemostatic treatment may still be needed on demand if a patient on Hemlibra suffers a trauma, needs a surgery or invasive procedure or suffers a breakthrough, spontaneous bleed.
- Hemlibra CANNOT be used to treat an acute bleed and a BPA or a Factor VIII replacement product such as Elocta is needed if the patient has bleeding due to a trauma or spontaneously or if an invasive procedure with a major risk of bleeding is needed.

Important information on the use of BPAs in patients on Hemlibra

- **The only BPA suitable for use in patients on Hemlibra is NovoSeven.**
- Feiba is relatively contraindicated due to the emergence of thrombosis and thrombotic microangiopathy in patients receiving Feiba at doses > 100 units/kg/24 hours in clinical trials. The use of Feiba must be authorised by a Consultant Haematologist at the patient's CCC.
- Antifibrinolytic therapy (Tranexamic acid 1 g TDS PO or IV) may be used in conjunction with Hemlibra and may be sufficient when used alone for minor bleeds or minor surgeries.

Important information on the use of Factor VIII in patients on Hemlibra

- **The preferred Factor VIII product for use in patients on Hemlibra is Elocta as there is a suitable FVIII assay to measure the infused FVIII in these patients.**
- Altuvoct is currently contraindicated due to the inability to be able to perform laboratory analysis of Factor VIII level when Hemlibra and Altuvoct are used together.
- Antifibrinolytic therapy (Tranexamic acid 1 g TDS PO or IV) may be used in conjunction with Hemlibra and may be sufficient when used alone for minor bleeds or minor surgeries.

Clearance of Hemlibra

- Hemlibra is an antibody, similar to IgG.
- The half- life of Hemlibra is approximately 4 weeks.
- If Hemlibra is stopped, the effects of Hemlibra on haemostasis and laboratory assays may persist for up to 6 months after the last dose.

Laboratory assays in patients on Hemlibra

- The APTT will shorten significantly in patients on Hemlibra, often into the lower end of the normal range or less than the lower limit of normal. This does NOT give an indication that haemostasis is "normal" and haemostatic treatment may still be needed for bleeding or prior to an invasive procedure.
- Factor VIII levels cannot be measured using a clotting Factor VIII assay (FVIII: C) as Hemlibra interferes with the assay and completely erroneous levels will be reported.
- Factor VIII assays and inhibitor screens can only be measured using a suitable chromogenic assay, provided in the National Coagulation Laboratory (NCL), St. James's Hospital – please contact the NCC and the NCL directly if lab testing is required.

Factor IX Deficiency (Haemophilia B)

General Information

Factor IX deficiency (Haemophilia B) is a bleeding disorder caused by a deficiency of clotting factor IX.
This condition affects around 1 in 25,000 to 30,000 males (about 5 times rarer than Haemophilia A). Female carriers of Haemophilia B may have low factor IX levels and one third have levels similar to mild Haemophilia i.e., 5-40% (0.05-0.40 IU/ml). These affected females may also need treatment for bleeding, menorrhagia or prior to surgery or labour and delivery.

Severity

Severity relates to the baseline level of factor IX.

Severity	Factor IX Activity Level
Severe disease	<1% (<0.01 IU/ml)
Moderate disease	1–5% (0.01-0.05 IU/ml)
Mild disease	>5% (>0.05 IU/ml)

Table 5 Factor IX Severity Categories

Treatment Administration

- **Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. i.e. Alprolix for FIX deficiency**
- **In doing so the Prescriber must note that not all patients with mild FIX deficiency require clotting factor concentrate and the use of alternative treatments may be indicated e.g. Tranexamic Acid**
- **The patient's treatment of choice must be confirmed with the relevant CCC.**

The Clinician should establish the treatment of choice i.e. Alprolix and/or Tranexamic Acid. Clotting Factor Concentrates for acute treatment are held in the Blood Transfusion department ofeach hospital.

Clotting Factor Concentrate - Alprolix

Please refer to product SPC for the most up to date information, advice and cautions.

Alprolix is the clotting factor concentrate used as the first line treatment and prophylaxis of bleeding in patients with FIX deficiency.
Alprolix comes as a powder with an accompanying solvent of sodium chloride solution.
Alprolix is administered as a bolus infusion.

Dose Calculation- Alprolix

The required dose must be determined by calculating the patient's weight and the required post treatment factor level that is determined by the severity and location of the bleed and the patient's clinical condition.

Bolus Dosing in FIX Deficiency CFC: Alprolix

Rise required = desired level of factor concentrate (%) minus baseline factor level (%)
(Note: 100% = 1.0 IU/ml, 50% = 0.5 IU/ml, 5% = 0.05 IU/ml)

$$\text{Dose required} = \frac{\text{Rise required (\%)} \times \text{Weight (kgs)}}{K}$$

K factor for FIX =1

Example -

A 50kg patient with a FIX: C <0.01 IU/ml (<1%) who needs a post factor level of 1.0 IU/ml (100%) will require 5000 units FIX concentrate. Round up to the nearest available vial size.

$$\frac{\textbf{100\% (1.0 IU/ml) – 0 \% (<0.01 IU/ml) x 50kg}}{\textbf{1}} \textbf{ = 5000 units}$$

Bleeding Site	**Target initial post treatment FIX Factor levels**
Major bleed	1.0 IU/ml (100%)
CNS or bleed involving peripheral nerve	1.0 IU/ml (100%)
Ileopsoas /retroperitoneal	1.0 IU/ml (100%)
Tongue/neck/retropharyngeal	1.0 IU/ml (100%)
Gastro-intestinal	1.0 IU/ml (100%)
Haemarthrosis	0.5 – 0.7 (50 - 70%) IU/ml
Minor bleed	0.5 IU/ml (50%)
Laceration requiring sutures	0.4 IU/ml (40%)
Haematuria	High fluid intake +/- rise to 0.3-0.5 IU/ml (30-50%)
Minor surgery (angiogram, lumbar puncture)	1.0 IU/ml (100%)
Liver biopsy or central venous catheter	1.0 IU/ml (100%)
Major surgery	1.0 IU/ml (100%)

Table 6: Desired Initial Post Treatment Factor Levels for Bleeds Types in Persons with FIX deficiency

Dose Administration- Alprolix

Alprolix should be:

- Administered as a slow intravenous push at a rate not exceeding 10ml per minute.
- A sample for post treatment factor level should be drawn 20 minutes' post administration (two coagulation samples sent to local laboratory for forwarding to the CCC for analysis).
- Liaise with CCC regarding the post treatment level result in case further treatment is required.

Tranexamic Acid (Cyklokapron)

Please refer to product SPC for the most up to date information, advice and cautions.

Tranexamic Acid is an anti-fibrinolytic agent, indicated in patients with haemophilia for short-term use (two to eight days), to reduce or prevent haemorrhage.
Tranexamic Acid is available in tablet and Intravenous Injection form.

Dose Calculation- Tranexamic Acid (Cyklokapron)

- **Oral** / Tablet form (500 mg Tranexamic Acid)
  Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- **Intravenous** Injection (500mg in 5ml ampoule)
  Recommended dose 10 mg/kg TDS

Dose administration- Tranexamic Acid (Cyklokapron)

Bolus injection – The required dose can be administered undiluted, very slowly i.e. at a rate of 100mg/min.
Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

Contraindications/Cautions- Tranexamic Acid (Cyklokapron)

Cyklokapron tablets are contraindicated in patients with:

- Severe renal impairment
- Subarachnoid haemorrhage
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Hypersensitivity to Tranexamic acid or any of the other ingredients.

Special warnings and precautions for use of Cyklokapron tablets:

- Reduction in dosage recommended in patients with renal insufficiency.
- Used with caution in patients with massive haematuria from the upper urinary tract.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use Cyklokapron tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use Cyklokapron Tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.

Cyklokapron solution for injection or infusion is contraindicated in patients with:

- Hypersensitivity to Tranexamic acid or any of the other ingredients.
- Acute venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding
- Severe renal impairment
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)
- Tranexamic Acid should not be administered by the intramuscular route

Special warnings and precautions for use of Cyklokapron solution for injection or infusion:

- Convulsions
- Visual Disturbances
- Haematuria
- Thromboembolic events
- Administer with care in patients receiving oral contraceptives because of increased risk of thrombosis
- Disseminated intravascular coagulation.

Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis).

Patients with Factor IX deficiency and inhibitors

- Inhibitors (antibodies against infused FIX concentrate) occur less commonly in FIX deficiency (Haemophilia B) in comparison to FVIII deficiency (Haemophilia A).
- The incidence of inhibitor development is approximately 3% and rarely occurs after 150 exposure days.
- A very small number of patients have persistent, high responding inhibitors and these

patients cannot receive FIX concentrate to treat or prevent bleeding but should receive alternative treatment with bypassing agents (see below).

- It is important to identify patients with FIX deficiency that have a current or past history of inhibitors.
- The presence of inhibitors in Factor IX deficiency may be associated with anaphylactoid reactions and the development of nephrotic syndrome.

In all cases where there is a history of an inhibitor, it is crucial to contact the patient's CCC to confirm the patient's optimal treatment regimen.

Critical information to be obtained is listed below and can be confirmed with the patient or on the patient's registration card from their Comprehensive Care Centre (CCC).

Important information on patients with a history of FIX inhibitors
Is inhibitor present currently or in past history?
What is patient's current treatment of choice?
Has patient ever received Immune tolerance treatment? If yes, when was this given and did the patient achieve eradication of the inhibitor?
Does the patient have a history of anaphylactoid reactions or of nephrotic syndrome following Factor IX administration?

Table 7: Important information on patients with a history of FIX inhibitors

Treatment options for patients with Factor IX patients with inhibitors

Bypassing Agents for Factor IX deficiency patients with inhibitors

Bypassing agents (BPA) are clotting factor concentrates designed to "bypass" the need for FIX and are given when the patient's inhibitor titre means that FIX concentrates will not be effective (high responding inhibitors).

Please refer to product SPC for the most up to date information, advice and cautions.

There are two bypassing agents available in Ireland:

- **Feiba** – an activated prothrombin complex concentrate (aPCC) containing factors II, VII, IX and X. The clotting factors are present in their inactive (zymogen) form and also in an activated form, as activation occurs as part of the manufacturing process. Feiba is derived from human blood donations and the product is dual virally inactivated.
- **NovoSeven** – recombinant activated factor VII (rFVIIa) can activate Factor X on the surface of activated platelets and thus, overcome the absence of FIX. The dose of activated factor VII is supra-physiological (about 10 times the normal level of FVII in the blood).
  NovoSeven is a fully recombinant clotting factor and does not contain human derived

material.

Cautions with Bypassing Agents in patients with Factor IX inhibitors

- Arterial and venous thrombotic complications have been reported during and after treatment with BPAs.
- Be aware of other risk factors for thrombosis in patients receiving BPAs and mitigate these where possible e.g., use of mechanical thromboprophylaxis if appropriate, avoidance of smoking, maintain ideal body weight, minimise periods of immobility.
- Use BPAs at the lowest effective dose and for the shortest duration possible when treating acute bleeding or managing invasive procedures.
- Avoid concomitant antifibrinolytic drugs e.g., Tranexamic acid unless advised by CCC. See also advice on dosing below.
- FIX inhibitors in patients with FIX deficiency have been associated with hypersensitivity reactions to infused FIX, including anaphylaxis and the development of nephrotic syndrome in some patients. As Feiba contains FIX, it is important to confirm whether the patient has ever experienced such a reaction before and avoid Feiba in this setting.
- For all patients, it is prudent to have appropriate treatments available for management of allergic reactions if administering Feiba in patients with FIX deficiency and inhibitors.

Dose Calculation of Bypassing Agents in patients with Factor IX inhibitors

BPA	**Initial dose**	**Subsequent dose and frequency**	**Important Notes**
Feiba	50-80 units/kg	50 units/kg every 8-12 hours	DO NOT EXCEED a total dose of 200 units/kgin a 24 hour period
Novoseven	90 micrograms/kg	90 micrograms/kg every 2-4 hours	

Table 8: Dose Calculation of Bypassing Agents for patients with Factor IX deficiency and inhibitors

Prophylaxis in Factor IX deficient patients with inhibitors

- BPAs may be used for prophylaxis as documented below.
- Feiba 50-80 units/kg IV three times per week
- NovoSeven 90 micrograms/kg three times per week or more frequently if required (may be given daily).

Von Willebrand Disease (VWD)

General Information

Von Willebrand Disease (VWD) is a bleeding disorder resulting from deficiency or abnormal function of Von Willebrand Factor (VWF).
VWF is a multimeric glycoprotein which has two main functions:

- To assist in platelet plug formation by binding circulating platelets to the site of vessel damage
- To bind to coagulation factor VIII preventing its clearance from the plasma

Disease Classification

VWD is subdivided into three types determined by the nature of the mutations in the *VWF* gene.
The 3 types are as follows:

- **Type 1 VWD**:
  Persons who have true Type 1 have levels of VWF antigen and/or activity of <0.3 IU/ml (activity level is measured by the Glycoprotein 1B M Activity level (GP1bM) or collagen binding (CBA) assays). FVIII may also be low.

- **Type 2 VWD:**
  Is further subdivided into types 2A, 2B, 2M, 2N.
  Type 2 VWD is characterised by abnormal function of the VWF protein and the GP1bM or CBA assays are lower than the VWF antigen in types 2A, 2B and 2M. Not all laboratories have access to the Gp1bM level. In such instances a VWF Ricof level can be used.
  In Type 2N VWD, the functional abnormality involves the binding of VWF to FVIII and the FVIII is low but the VWF levels may not be low.

- **Type 3 VWD**: Persons with Type 3 have very low levels of VWF and FVIII and have the most severe bleeding phenotype which is akin to severe Haemophilia.

In addition, the following subcategories are recognised

- **Low VWF**: This relates to persons who have low VWF levels between 0.3 and 0.5 IU/ml. The low levels are not only caused by mutations in the gene for VWF but VWF levels may be reduced in a number of ways including for example by faster clearance of the VWF protein from the blood as happens in people who are blood group O.
  Some people with low VWF levels have bleeding symptoms and may need to have preventative treatment if they are having surgery or other invasive procedures.

- **Platelet-type VWD** is a rare condition caused by a mutation in the glycoprotein on the surface of platelets which interacts with VWF.

Severity

The severity relates to the VWF level and activity.

	VWF antigen and /or activity	**Clinical bleeding phenotype**
Low VWF	0.3-0.5 IU/ml	Some patients may bleed with invasive procedures, or have menorrhagia or mucocutaneous bleeding
Type 1	<0.3 IU/ml	Bleeding after invasive dental or surgical procedures, menorrhagia, mucocutaneous bleeding
Type 2	<0.3 IU/ml (GP1bM or CBA) Ratio of activity to antigen <0.5-0.7	Variable bleeding tendency.
Type 3	Levels are very low or undetectable	Mucocutaneous bleeding, menorrhagia, post-operative bleeding. May have haemarthrosis, muscle haematomas

Table 9: The severity and associated presentation of VWF level and activity

Treatment Administration

- **Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. Wilate or Veyvondi for VWD**
- **In doing so the Prescriber must note that not all patients VWD or with low VWF require clotting factor concentrate and the use of alternative treatments may be indicated e.g. Desmopressin and/or Tranexamic Acid**
- **The patient's treatment of choice must be confirmed with the relevant CCC.**

- Minor bleeding involving mucosal surfaces of the nose, mouth or female genital tract can be treated with Tranexamic acid alone.
- Excessive menstrual bleeding can be treated with the addition of hormonal therapy e.g. the combined oral contraceptive pill or progesterone only pill or consideration can be given to progesterone releasing intra-uterine system (Mirena).
- For more extensive or major bleeding, Desmopressin or VWF concentrate should be used. The choice of agent will depend on the age of the patient, the presence of or risk factors for

arteriovascular disease and the documented response of the patient to Desmopressin. The CCC willadvise on the appropriate treatment to use.

- The Clinician should establish the treatment of choice i.e., Wilate, Veyvondi Desmopressin Injection and/or Tranexamic Acid.
- Clotting Factor Concentrates are held in the Blood Transfusion department of each hospital.

The selected treatment should be prepared and administered as follows:

Clotting Factor Concentrate- Wilate

Please refer to product SPC for the most up to date information, advice and cautions.

Wilate is the clotting factor concentrate recommended for use in the prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD)

Dose Calculation- Wilate

The required dose must be determined by calculating the patient's weight and the required post treatment factor level which is determined by the severity and location of the bleed and the patient's clinical condition (Please contact patients Consultant Haematologist in their CCC).
Wilate comes as a powder and should be reconstituted using the accompanying solvent (i.e., water for injections with 0.1 % Polysorbate 80) which comes with a NEXTARO transfer device™.
Wilate should be reconstituted using aseptic technique in accordance with the Wilate reconstitution procedure.

Rise required = desired level of factor concentrate (%) minus baseline GP1bM level

(%)Note: 100% = 1.0 IU/ml, 50% = 0.5 IU/ml, 5% = 0.05 IU/ml)

$$\text{Dose required} = \frac{\text{Rise Required (\%)} \times \text{Weight (kgs)}}{\text{K}}$$

K factor for Wilate calculation = 2

$$\frac{100\%\ (1.0\ \text{IU/ml}) - 12\ \%\ (<0.12\ \text{IU/ml}) \times 50\text{kg}}{2} = 2200\ \text{units}$$

Example:

A 50kg patient with a GP1bM level <0.12 IU/ml (12%) who needs a post level of 1.0 IU/ml (100%) will require2200 units concentrate. Round to up to the nearest available vial size= 2500units.

Dose Administration- Wilate

- Factor concentrate should be administered as a slow intravenous push, not exceeding 3 mls per minute
- A post treatment factor level should be drawn 20 minutes' post administration (four coagulation samples, send to local laboratory for forwarding to the CCC for analysis)
- Liaise with CCC regarding the post treatment level result in case further treatment is required.

Clotting Factor Concentrate- Veyvondi

Please refer to product SPC for the most up to date information, advice and cautions

Veyvondi is the recombinant clotting factor concentrate recommended for use in the prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD) in adults aged 18 and over. On occasion when a patient with Von Willebrand disease has an associated low Factor VIII level < 0.40 IU/ml (<40%) and if there is an urgent requirement for treatment for a severe bleed or emergency surgery there may be a requirement to co-administer recombinant Factor VIII (rFVIII) concentrate following the first infusion of Veyvondi.

Dose Calculations- Veyvondi

The required dose must be determined by calculating the patient's weight and the required post treatment factor level which is determined by the severity and location of the bleed and the patient's clinical condition (Please contact patients Consultant Haematologist in their CCC)

Veyvondi comes as a powder and should be reconstituted using the accompanying solvent. The transfer device for the reconstitution of Veyvondi is the Mix2Vial

Veyvondi should be reconstituted using aseptic technique in accordance with the Veyvondi reconstitution procedure

Veyvondi is available in the following vial sizes: 1300-unit vial & 650-unit vial

Rise required= desired level of factor concentrate (%) minus baseline GP1bM Level

(%)Note: 100% = 1.0 IU/ml, 50%= 0. 5 IU/ml and 5%= 0.05 IU/ml

$$\text{Dose required} = \frac{\text{Rise required (\%)} \times \text{Weight (Kg)}}{K}$$

K Factor of Veyvondi calculation= 2

$$\frac{100\% (1.0\text{iu/ml}) - 18\% (0.18\ \text{IU/ml}) \times 75\text{kg}}{2} = 3075\ \text{units}$$

Example:
A 75kg patient with a GP1bM level of 0.18 IU/ML (18%) who needs a post level of 1.0 IU/Ml (100%)will require 3075 units. Round up to the nearest vials for Veyvondi 3250 units
Veyvondi vials required: 1300iu vial x 2 & 650iu vial x 1

Dose Administration- Veyvondi

- Veyvondi should be administered as a slow intravenous push, not exceeding 4 ml per minute
- The reconstituted solution should be allowed to stand for 5 minutes and then gently swirled before drawing it up in to a plastic syringe
- It is not uncommon for a few flakes or particles to remain in the product vial after reconstitution. The filter within the Mix2Vial device will prevent the particles from transferring to the syringe. You should not use the product if the solution in the syringe appears cloudy or contains flakes or particles after filtration
- If you need to co-administer rFVIII, the rFVIII should be administered within 10 minutes of the infusion of Veyvondi being administered
- A post treatment factor level should be drawn 20 minutes' post administration (four coagulation samples send to local laboratory for forwarding to the CCC for analysis.
- Liaise with the CCC regarding the post treatment level in case further treatment is required

Desmopressin

Please refer to product SPC for the most up to date information, advice and cautions.

Desmopressin solution for injection (Desmopressin Acetate) is a synthetic analogue of the natural hormone arginine vasopressin. It is indicated for use in managing bleeds in some persons with Factor VIII deficiency and Von Willebrand disease/Low VWF by increasing plasma levels of FVIII and VWF.

Dose Calculation- Desmopressin

Desmopressin can be administered intravenously or subcutaneously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.
There are two product forms available for Desmopressin; DDAVP (intravenous only) or Octim (subcutaneous or intravenous use)

Example: A 60kg patient requiring DDAVP, the dose should be calculated as 60 kg x 0.3 micrograms = 18 micrograms.

Dose Administration- Desmopressin

DDAVP which is **only for intravenous use**, comes in 1ml ampoule which contains Desmopressin acetate **4 micrograms per ml** in asterile, aqueous solution for injection
DDVAP should be added to 50mls of normal saline using an aseptic technique.
The 50ml solution should be administered intravenously over 20 minutes.
Example: A 60kg patient requiring DDAVP - The intravenous preparation has a concentration of 4 micrograms /ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 4.5mls of DDAVP in 50mls of normal saline and this will be administered IV over 20 minutes.

Octim which is the desmopressin form for subcutaneous injection and intravenous use comes in 1ml which contains 15 micrograms per ml

The subcutaneous preparation has a concentration of 15 micrograms/ml. Therefore, the subcutaneous dose for a 60kg patient (18 micrograms) would be prepared by drawing up 1.2 mls of Octim in to a syringe and administered subcutaneously

Octim can also be administered intravenously. The intravenous preparation has a concentration of 15 micrograms per ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 1.2ml of Octim in 50mls of normal saline and this will be administered IV over 20 minutes

Desmopressin is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in the SPC
- Habitual or psychogenic polydipsia
- A history of unstable angina and/or known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion (SIADH)
- Von Willebrands disease type II B where the administration of Desmopressin may result in pseudothrombocytopenia due to the release of clotting factors which cause platelet aggregation

Special warnings and precautions for use:

Fluid balance

- Desmopressin should only be administered under the supervision of a specialist with appropriatelaboratory facilities available for monitoring of the patient.
- It is recommended to maintain fluid and electrolyte balance. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatraemia

with or without accompanying warning signs or symptoms. Local practice is to ensure no more than 1.5 litres total fluid intake in adults in 24 hours post Desmopressin infusion.

- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia Treatment with Desmopressin should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis) as well as in excessive bleeding, and the fluid and electrolyte balance should be carefully monitored.
- Special attention should be given when Desmopressin is co-administered with other drugs affecting water and or sodium homeostasis. In patients with chronic therapy with drugs affecting water and/or sodium homeostasis, Desmopressin Injection should be administered after confirmation of normal baseline sodium.
- When repeated doses are used to control bleeding in haemophilia or von Willebrands disease, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or determining plasma sodium or osmolality.

Thrombotic Risk

- Due to post marketing reports, with Desmopressin injection, of deep vein thrombosis, cerebrovascular accident and disorder (Stroke), cerebral thrombosis, myocardial infarction, angina pectoris and chest pain, considerations should be taken before using Desmopressin injection in elderly patents and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice Desmopressin is not usually recommended for patients > 55years.

Other Conditions

- Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.
- The benefits of Desmopressin versus other haemostatic therapies should be carefully assessed in situations where prolonged haemostasis is required including active post-operative bleeding and variceal bleeding in patients with cirrhosis
- Continuous blood pressure monitoring is recommended during infusion of Desmopressin Injection
- Precautions must be taken in patients at risk for increased intra cranial pressure.
- Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50ml/min)

Tranexamic Acid (Cyklokapron)

Please refer to product SPC for the most up to date information, advice and cautions.

Tranexamic Acid is an anti-fibrinolytic agent, indicated in patients with haemophilia for short-term use (two to eight days), to reduce or prevent haemorrhage.
Tranexamic Acid is available in tablet and Intravenous Injection form.

Dose Calculation- Tranexamic Acid (Cyklokapron)

- **Oral** / Tablet form (500 mg Tranexamic Acid)
  Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- **Intravenous** Injection (500mg in 5ml ampoule)
  Recommended dose 10 mg/kg TDS

Dose administration- Tranexamic Acid (Cyklokapron)

Bolus injection – The required dose can be administered undiluted, very slowly i.e., at a rate of 100mg/min.
Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

Contraindications/Cautions- Tranexamic Acid (Cyklokapron)Cyklokapron tablets are contraindicated in patients with:

- Severe renal impairment
- Subarachnoid haemorrhage
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Hypersensitivity to Tranexamic acid or any of the other ingredients.

*Special warnings and precautions for use of **Cyklokapron tablets:***

- Reduction in dosage recommended in patients with renal insufficiency.
- Use with caution in patients with massive haematuria from the upper urinary tract.
- Use with caution when intravascular coagulation is in progress.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use Cyklokapron tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use Cyklokapron Tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.

Cyklokapron solution for injection or infusion *is contraindicated in patients with:*

- Hypersensitivity to Tranexamic acid or any of the other ingredients.
- Acute venous or arterial thrombosis.
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding.
- Severe renal impairment.
- History of convulsions.
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions).
- Tranexamic Acid should not be administered by the intramuscular route.

Special warnings and precautions for use of ***Cyklokapron solution for injection or infusion:***

- Convulsions
- Visual Disturbances
- Haematuria
- Thromboembolic events
- Administer with care in patients receiving oral contraceptives because of increased risk of thrombosis
- Disseminated intravascular coagulation.

Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis).

Platelet Function Disorders

General Information

- Platelet function disorders (PFDs) are a heterogeneous group of conditions affecting the function of platelets in primary haemostasis.
- Inherited PFDs may be caused by specific genetic mutations e.g., Glanzmann'sThrombasthenia or Bernard Soulier Syndrome.
- More often, the genetic cause of the PFD is not known and the conditions are described as Non-Specific PFDs.
- Persons with PFDs are likely to present with symptoms of mucocutaneous bleeding including recurrent epistaxis, easy bruising, excessive bleeding after dental extraction or surgery, menorrhagia and post-partum haemorrhage in women.
- There are a variety of treatment options for platelet function disorders.
- The patient's CCC must be contacted to determine the optimal treatment for each patient and clinical scenario.

Severity

- The severity of the bleeding disorder is variable and the patient's previous bleeding history will be informative, e.g., response to previous haemostatic challenges.
- Certain PFDs are very likely to be associated with a bleeding phenotype e.g., Glanzmann'sthrombasthenia or Bernard Soulier syndrome.
- The patient's CCC will be able to advise on the bleeding severity for individual patients.

Treatment Administration

Prescribers must ensure that they prescribe the correct treatment. Treatment options include the use of the following:

- **Random Donor Platelets**
- **Human Leukocyte Antigen (HLA) Matched Platelets**
- **Recombinant Factor VIIa**
- **Desmopressin Tranexamic Acid**

The prescriber must note that not all patients with PFDs require platelet transfusion and the use of alternative treatments may be indicated e.g., Desmopressin or Tranexamic Acid

The patient's treatment of choice must be confirmed with the relevant CCC.

The Clinician should establish the treatment of choice in consultation with the CCC and prepare and administer as follows:

Platelet Transfusion

- Where platelet transfusion is indicated the Clinician should order, prescribe and administer platelets in accordance with local protocols.
- Where the CCC directs that the use of HLA matched platelets is indicated they must be ordered from the Irish Blood Transfusion Service.

Recombinant Factor VIIa/NovoSeven

Please refer to product SPC for the most up to date information, advice and cautions.

Recombinant Factor VIIa / Novo Seven is a factor concentrate indicated for use to control bleeding in some cases of PFD.

Dose Calculation- Recombinant Factor VIIa/NovoSeven

- The required initial dose is usually 90 micrograms /kg body weight.
- Establish the **Recombinant Factor VIIa / NovoSeven** dose required in consultation with the Consultant Haematologist on-call at the CCC.

Dose Administration- Recombinant Factor VIIa/NovoSeven

- Recombinant Factor VIIa / NovoSeven come as a powder and a solvent in a pre-filled syringe which must be reconstituted for solution.
- Recombinant Factor VIIa / NovoSeven should be reconstituted using aseptic technique in accordance with the Reconstituted Procedure.
- Pre filled glass syringes are not compatible with clave connectors, therefore if administering NovoSeven via a clave connector, PICC line or CVAD; you should draw the reconstituted solution in to a plastic syringe prior to administration.
- Clotting factor concentrate should be administered as a slow intravenous push over 2 to 5 minutes.

- There is no requirement for monitoring of NovoSeven therapy. Severity of bleeding condition and clinical response to NovoSeven administration must guide dosing requirements.
- Liaise with CCC regarding on-going management requirements.

Desmopressin

Please refer to product SPC for the most up to date information, advice and cautions.

Desmopressin solution for injection (Desmopressin Acetate) is a synthetic analogue of the natural hormone arginine vasopressin. It is indicated for use in managing bleeds in some persons with Factor VIII deficiency and Von Willebrand disease/Low VWF by increasing plasma levels of FVIII and VWF.

Dose Calculation- Desmopressin

Desmopressin can be administered intravenously or subcutaneously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.
There are two product forms available for Desmopressin; DDAVP (intravenous only) or Octim (subcutaneous or intravenous use)

Example: A 60kg patient requiring Desmopressin, the dose should be calculated as 60 kg x 0.3 micrograms = 18 micrograms.

Dose Administration- Desmopressin

DDAVP which is **only for intravenous use**, comes in 1ml ampoule which contains Desmopressin acetate **4 micrograms per ml** in asterile, aqueous solution for injection
DDVAP should be added to 50mls of normal saline using an aseptic technique.
The 50ml solution should be administered intravenously over 20 minutes.
Example: A 60kg patient requiring DDAVP - The intravenous preparation has a concentration of 4 micrograms /ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 4.5mls of DDAVP in 50mls of normal saline and this will be administered IV over 20 minutes.

Octim which is the desmopressin form for subcutaneous injection and intravenous use comes in 1ml which contains 15 micrograms per ml

The subcutaneous preparation has a concentration of 15 micrograms/ml. Therefore, the subcutaneous dose for a 60kg patient (18 micrograms) would be prepared by drawing up 1.2 mls of Octim in to a syringe and administered subcutaneously.

Octim can also be administered intravenously. The intravenous preparation has a concentration of 15 micrograms per ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 1.2ml of Octim in 50mls of normal saline and this will be administered IV over 20 minutes

Contraindications/Cautions- Desmopressin

Desmopressin is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in the SPC
- Habitual or psychogenic polydipsia
- A history of unstable angina and/or known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion (SIADH)
- Von Willebrands disease type II B where the administration of Desmopressin may result in pseudothrombocytopenia due to the release of clotting factors which cause platelet aggregation

Special warnings and precautions for use:

Fluid balance

- Desmopressin should only be administered under the supervision of a specialist with appropriatelaboratory facilities available for monitoring of the patient.
- It is recommended to maintain fluid and electrolyte balance. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatraemia with or without accompanying warning signs or symptoms. Local practice is to ensure no more than 1.5 litres total fluid intake in adults in 24 hours post Desmopressin infusion.
- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia Treatment with Desmopressin should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis) as well as in excessive bleeding, and the fluid and electrolyte balance should be carefully monitored.
- Special attention should be given when Desmopressin is co-administered with other drugs affecting water and or sodium homeostasis. In patients with chronic therapy with drugs affecting water and/or sodium homeostasis, Desmopressin Injection should be administered after confirmation of normal baseline sodium.
- When repeated doses are used to control bleeding in haemophilia or von Willebrands disease, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or determining plasma sodium or osmolality.

Thrombotic Risk

- Due to post marketing reports, with Desmopressin injection, of deep vein thrombosis, cerebrovascular accident and disorder (Stroke), cerebral thrombosis, myocardial infarction, angina pectoris and chest pain, considerations should be taken before using Desmopressin injection in elderly patents and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice Desmopressin is not usually recommended for patients > 55years.

Other Conditions

- Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.
- The benefits of Desmopressin versus other haemostatic therapies should be carefully assessed in situations where prolonged haemostasis is required including active post-operative bleeding and variceal bleeding in patients with cirrhosis
- Continuous blood pressure monitoring is recommended during infusion of Desmopressin Injection
- Precautions must be taken in patients at risk for increased intra cranial pressure.
- Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50ml/min)

Tranexamic Acid (Cyklokapron)

ease refer to product SPC for the most up to date information, advice and cautions.

Tranexamic Acid is an anti-fibrinolytic agent, indicated in patients with haemophilia for short-term use (two to eight days), to reduce or prevent haemorrhage.
Tranexamic Acid is available in tablet and Intravenous Injection form.

Dose Calculation- Tranexamic Acid (Cyklokapron)

- **Oral** / Tablet form (500 mg Tranexamic Acid)
  Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- **Intravenous** Injection (500mg in 5ml ampoule)
  Recommended dose 10 mg/kg TDS

Dose administration- Tranexamic Acid (Cyklokapron)

Bolus injection – The required dose can be administered undiluted, very slowly i.e., at a rate of 100mg/min.
Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

Contraindications/Cautions- Tranexamic Acid (Cyklokapron)

Cyklokapron tablets are contraindicated in patients with:

- Severe renal impairment
- Subarachnoid haemorrhage
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Hypersensitivity to Tranexamic acid or any of the other ingredients.

Special warnings and precautions for use of Cyklokapron tablets:

- Reduction in dosage recommended in patients with renal insufficiency.
- Use with caution in patients with massive haematuria from the upper urinary tract.
- Use with caution when intravascular coagulation is in progress.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use Cyklokapron tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use Cyklokapron Tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.

Cyklokapron solution for injection or infusion is contraindicated in patients with:

- Hypersensitivity to Tranexamic acid or any of the other ingredients.
- Acute venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding
- Severe renal impairment
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)
- Tranexamic Acid should not be administered by the intramuscular route

Special warnings and precautions for use of Cyklokapron solution for injection or infusion:

- Convulsions
- Visual Disturbances
- Haematuria
- Thromboembolic events
- Administer with care in patients receiving oral contraceptives because of increased risk of thrombosis
- Disseminated intravascular coagulation.

Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis).

Rare Bleeding Disorders

General Information

Rare bleeding disorders (RBDs) include deficiencies of factors I (Fibrinogen), II, V, VII, X, XI and XIII. These deficiencies can be severe or mild. Severe deficiencies may present with bleeding symptoms similar to haemophilia. Not all mild deficiencies are associated with bleeding but the bleeding tendency may be variable in some RBDs. Expert advice from a CCC is **always** required.

Severity

Severity relates to the baseline level of the deficient factor but in some deficiencies, the patient's personal bleeding history may need to be considered. The patient's CCC will be able to advise on the bleeding severity for an individual patient.

Deficient Factor	Normal Reference Interval (NCC, St James's Hospital)	Severe Deficiency	Mild Deficiency
Fibrinogen	1.9-3.5 g/L	Undetectable	<1.5g/L
Prothrombin	0.72-1.31 IU/ml	< 0.10 IU/ml	0.10-0.71 IU/ml
V	0.63-1.33 IU/ml	<0.10 IU/ml	0.10-0.62 IU/ml
VII	0.51-1.54 IU/ml	<0.10 IU/ml	0.10-0.50 IU/ml
X	0.64-1.50 IU/ml	<0.01 IU/ml	0.06-0.63 IU/ml
XI	0.72-1.52 IU/ml	<0.20 IU/ml	0.20-0.70 IU/ml
XIII	0.73-1.60 IU/ml	<0.10 IU/ml	0.10-0.73 IU/ml

Table 10: Rare bleeding disorders and factor deficiencies- Severity Categories

Treatment Administration

- **Prescribers must ensure that they prescribe the correct factor replacement treatment, if indicated (See Table 11 below)**
- **The prescriber must note that not all patients with mild rare bleeding disorders require factor replacement and the use of alternative treatments may be indicated e.g., Tranexamic Acid**
- **The patient's treatment of choice must be confirmed with the relevant CCC.**

The deficiency type will determine the appropriate factor replacement treatment to be used – See Table 11 below.

Deficiency	Factor Replacement Treatment (If indicated)
Fibrinogen	Fibryga (Fibrinogen concentrate)
Factor II	Octaplex (Prothrombin complex concentrate)
Factor V	Octaplas (Solvent detergent treated frozen plasma)
Factor VII	NovoSeven (Recombinant factor VIIa)
Factor X	Coagadex (Factor X Concentrate))
Factor XI	Octaplas (Solvent detergent treated frozen plasma)
Factor XIII	Fibrogammin (FXIII concentrate)

Table 11: Rare Bleeding Disorders – CFC treatments

The Clinician should establish the treatment of choice with CFC, solvent detergent treated frozen plasma or Tranexamic Acid.
Clotting Factor Concentrates are held in the Blood Transfusion department of each hospital.

Dose Calculation- Clotting Factor Concentrate

The required dose must be determined by calculating the patient's weight and the required post treatment factor level which is determined by the severity and location of the bleed.
Please discuss with the CCC (see Appendix 1: Quick Reference: How to calculate an initial dose of clotting factor concentrate).
Clotting Factor Concentrate must be reconstituted for use using an aseptic technique (Refer to Factor Reconstitution Procedure – (see Appendix 2: Quick reference: Administration information on Clotting Factor Concentrates)

Dose Administration- CFC

- Factor concentrate should be administered as a slow intravenous push over 5 minutes.
- A post treatment factor level should be drawn 20 minutes' post administration (two coagulation samples sent to local laboratory for forwarding to the CCC for analysis).
- Liaise with CCC regarding the post treatment level result in case further treatment is required.

Tranexamic Acid (Cyklokapron)

Please refer to product SPC for the most up to date information, advice and cautions.

Tranexamic Acid is an anti-fibrinolytic agent, indicated in patients with haemophilia for short-term use (two to eight days), to reduce or prevent haemorrhage.
Tranexamic Acid is available in tablet and Intravenous Injection form.

Dose Calculation- Tranexamic Acid (Cyklokapron)

- **Oral** / Tablet form (500 mg Tranexamic Acid)
  Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- **Intravenous** Injection (500mg in 5ml ampoule)
  Recommended dose 10 mg/kg TDS

Dose administration- Tranexamic Acid (Cyklokapron)

Bolus injection – The required dose can be administered undiluted, very slowly i.e. at a rate of 100mg/min.
Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

Contraindications/Cautions- Tranexamic Acid (Cyklokapron)Cyklokapron tablets are contraindicated in patients with:

- Severe renal impairment
- Subarachnoid haemorrhage
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Hypersensitivity to Tranexamic acid or any of the other ingredients.

Special warnings and precautions for use of Cyklokapron tablets:

- Reduction in dosage recommended in patients with renal insufficiency.
- Use with caution in patients with massive haematuria from the upper urinary tract.
- Use with caution when intravascular coagulation is in progress.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use Cyklokapron tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use Cyklokapron Tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.

Cyklokapron solution for injection or infusion is contraindicated in patients with:

- Hypersensitivity to Tranexamic acid or any of the other ingredients.
- Acute venous or arterial thrombosis

- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding
- Severe renal impairment
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)
- Tranexamic Acid should not be administered by the intramuscular route

Special warnings and precautions for use of Cyklokapron solution for injection or infusion:

- Convulsions
- Visual Disturbances
- Haematuria
- Thromboembolic events
- Administer with care in patients receiving oral contraceptives because of increased risk of thrombosis
- Disseminated intravascular coagulation.

Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis).

Clotting Factor Concentrate - Coagadex

Please refer to product SPC for the most up to date information, advice and cautions

Coagadex is the plasma clotting factor concentrate recommended for use in the prevention and treatment of haemorrhage or surgical bleeding in individuals with Factor X deficiency (FX)

Dose Calculations- Coagadex

The required dose must be determined by calculating the patient's weight and the required post treatment factor level which is determined by the severity and location of the bleed and the patient's clinical condition (Please contact patients Consultant Haematologist in their CCC)

Coagadex comes as a powder and should be reconstituted using the accompanying solvent. The transfer device for the reconstitution of Coagadex is the Mix2Vial transfer device

Coagadex should be reconstituted using aseptic technique in accordance with the Veyvondi reconstitution procedure

Coagadex is available in the following vial sizes: 250-unit vial & 500-unit vial

***The max daily dosing of Coagadex across all age groups is 60 IU/kg

Rise required= desired level of factor concentrate (%) minus baseline Factor X Level (%)

Note: 100% = 1.0 IU/ml, 50%= 0. 5 IU/ml and 5%= 0.05 IU/ml

$$\text{Dose required} = \frac{\text{Rise required (\%)} \times \text{Weight (Kg)}}{K}$$

K Factor of Coagadex calculation= 2

$$\frac{90\% \text{ (0.9iu/ml)} - 1\% \text{ (0.01 IU/ml)} \times 72\text{kg}}{} = 3204 \text{ units}$$

Example:
A 72kg patient with a Factor X level of 0.01 IU/ML (1%) who needs a post level of 0.9 IU/Ml (90%) will require 3204 units. Round up to the nearest vials for Coagadex 3250 units
Coagadex vials required: 500iu vial x 6 & 250iu vial x 1

Dose Administration- Coagadex

- Coagadex should be administered as a slow intravenous push a suggested rate of 10 ml per minute but not exceeding 20 ml per minute
- A post treatment factor level should be drawn 20 minutes' post administration (four coagulation samples send to local laboratory for forwarding to the CCC for analysis.
- Liaise with the CCC regarding the post treatment level in case further treatment is required.

Bleeding Disorder of Unknown Cause

General Information

The diagnosis of bleeding disorder of unknown cause (BDUC) may be assigned to patients with a history of severe and/or recurrent bleeding after invasive procedures or haemostatic challenges such as childbirth.

This diagnosis is assigned after the patient has had review in a specialist Coagulation centre and has had a full haemostatic work up done, including assessment of coagulation factor levels and platelet function.

The diagnosis is assigned when the patient is found to have a significant history of bleeding but no abnormalities are found on laboratory testing. These patients are at risk of increased bleeding in the future and may require haemostatic treatment before invasive procedures or delivery.

Severity

Severity of BDUC is variable and is determined by the patient's clinical bleeding history.

Treatment Administration

Prescribers must ensure that they prescribe the correct treatment. Treatment options include the use of the following:

- **Tranexamic Acid**

Desmopressin If severe bleeding, consider random donor platelets or

recombinant factor VIIa.The patient's treatment of choice must be confirmed

with the relevant CCC.

Tranexamic Acid (Cyklokapron)

Please refer to product SPC for the most up to date information, advice and cautions.

Tranexamic Acid is an anti-fibrinolytic agent, indicated in patients with haemophilia for short- term use (two to eight days), to reduce or prevent haemorrhage.

Tranexamic Acid is available in tablet and Intravenous Injection form.

Dose Calculation- Tranexamic Acid (Cyklokapron)

- **Oral** / Tablet form (500 mg Tranexamic Acid)
  Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- **Intravenous** Injection (500mg in 5ml ampoule)
  Recommended dose 10 mg/kg TDS

Dose administration- Tranexamic Acid (Cyklokapron)

Bolus injection – The required dose can be administered undiluted, very slowly i.e. at a rate of 100mg/min.
Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

Contraindications/Cautions- Tranexamic Acid (Cyklokapron)Cyklokapron tablets are contraindicated in patients with:

- Severe renal impairment
- Subarachnoid haemorrhage
- History of venous or arterial thrombosis
- Fibrinolytic conditions following consumption coagulopathy
- History of convulsions
- Hypersensitivity to Tranexamic acid or any of the other ingredients.

Special warnings and precautions for use of Cyklokapron tablets:

- Reduction in dosage recommended in patients with renal insufficiency.
- Use with caution in patients with massive haematuria from the upper urinary tract.
- Use with caution when intravascular coagulation is in progress.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use Cyklokapron tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use Cyklokapron Tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.

Cyklokapron solution for injection or infusion is contraindicated in patients with:

- Hypersensitivity to Tranexamic acid or any of the other ingredients.
- Acute venous or arterial thrombosis

- Fibrinolytic conditions following consumption coagulopathy except in those with predominant activation of the fibrinolytic system with acute severe bleeding
- Severe renal impairment
- History of convulsions
- Intrathecal and intraventricular injection, intracerebral application (risk of cerebral oedema and convulsions)
- Tranexamic Acid should not be administered by the intramuscular route

Special warnings and precautions for use of Cyklokapron solution for injection or infusion:

- Convulsions
- Visual Disturbances
- Haematuria
- Thromboembolic events
- Administer with care in patients receiving oral contraceptives because of increased risk of thrombosis
- Disseminated intravascular coagulation.

Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis).

Desmopressin

Please refer to product SPC for the most up to date information, advice and cautions.

Desmopressin solution for injection (Desmopressin Acetate) is a synthetic analogue of the natural hormone arginine vasopressin. It is indicated for use in managing bleeds in some persons with Factor VIII deficiency and Von Willebrand disease/Low VWF by increasing plasma levels of FVIII and VWF.

Dose Calculation- Desmopressin

Desmopressin can be administered intravenously or subcutaneously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.
There are two product forms available for Desmopressin; DDAVP (intravenous only) or Octim (subcutaneous or intravenous use)

Example: A 60kg patient requiring Desmopressin, the dose should be calculated as 60 kg x 0.3 micrograms = 18 micrograms.

Dose Administration- Desmopressin

DDAVP which is **only for intravenous use**, comes in 1ml ampoule which contains Desmopressin acetate **4 micrograms per ml** in asterile, aqueous solution for injection.

DDVAP should be added to 50mls of normal saline using an aseptic technique.
The 50ml solution should be administered intravenously over 20 minutes.
Example: A 60kg patient requiring DDAVP - The intravenous preparation has a concentration of 4 micrograms /ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 4.5mls of DDAVP in 50mls of normal saline and this will be administered IV over 20 minutes.

Octim which is the desmopressin form for both subcutaneous injection and intravenous use comes in 1ml which contains 15 micrograms per ml

The subcutaneous preparation has a concentration of 15 micrograms/ml. Therefore, the subcutaneous dose for a 60kg patient (18 micrograms) would be prepared by drawing up 1.2 mls of Octim in to a syringe and administered subcutaneously

Octim can also be administered intravenously. The intravenous preparation has a concentration of 15 micrograms per ml. Therefore, the intravenous dose for a 60kg patient (18 micrograms) will be prepared by diluting 1.2ml of Octim in 50mls of normal saline and this will be administered IV over 20 minutes

Desmopressin is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in the SPC
- Habitual or psychogenic polydipsia
- A history of unstable angina and/or known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Known hyponatremia
- Syndrome of inappropriate ADH secretion (SIADH)
- Von Willebrands disease type II B where the administration of Desmopressin may result in pseudothrombocytopenia due to the release of clotting factors which cause platelet aggregation

Special warnings and precautions for use:

Fluid balance

- Desmopressin should only be administered under the supervision of a specialist with appropriatelaboratory facilities available for monitoring of the patient.
- It is recommended to maintain fluid and electrolyte balance. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatraemia with or without accompanying warning signs or symptoms. Local practice is to ensure no more than 1.5 litre total fluid intake in adults in 24 hours post Desmopressin infusion.
- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia Treatment with Desmopressin should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or

electrolyte imbalance (such as systemic infections, fever, gastroenteritis) as well as in excessive bleeding, and the fluid and electrolyte balance should be carefully monitored.

- Special attention should be given when Desmopressin is co-administered with other drugs affecting water and or sodium homeostasis. In patients with chronic therapy with drugs affecting water and/or sodium homeostasis, Desmopressin Injection should be administered after confirmation of normal baseline sodium.
- When repeated doses are used to control bleeding in haemophilia or von Willebrands disease, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or determining plasma sodium or osmolality.

Thrombotic Risk

- Due to post marketing reports, with Desmopressin injection, of deep vein thrombosis, cerebrovascular accident and disorder (Stroke), cerebral thrombosis, myocardial infarction, angina pectoris and chest pain, considerations should be taken before using Desmopressin injection in elderly patents and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice Desmopressin is not usually recommended for patients > 55years.

Other Conditions

- Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.
- The benefits of Desmopressin versus other haemostatic therapies should be carefully assessed in situations where prolonged haemostasis is required including active post-operative bleeding and variceal bleeding in patients with cirrhosis
- Continuous blood pressure monitoring is recommended during infusion of Desmopressin Injection
- Precautions must be taken in patients at risk for increased intra cranial pressure.
- Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50ml/min)

Management of Allergic Reaction to Treatment

Clotting Factor Concentrates

In the event of a reaction or suspected reaction the Clinician should undertake the following:

- Discontinue the Factor Concentrate
- Assess the patient
- Contact the relevant CCC for advice on alternative treatments
- Report reactions as per your local hospital drug reaction policy

In the event of **mild to moderate reaction** the Clinician should undertake the following:

- Administer Chlorpheniramine 10-20 mg IM or slow IV (at least over one minute)
- If required, add Hydrocortisone 100 - 200mg slow IV (over three minutes)

In the event of **severe allergic or anaphylactic reaction** should be managed in accordance with the guidance from the National Immunisation Advisory Committee (NIAC, 2023).

Desmopressin

Please refer to product SPC for the most up to date information, advice and cautions.

Reactions to Desmopressin

Reactions to Desmopressin can be common

Mild reactions to Desmopressin commonly include the following:

- Vasodilatation
- Hypotension
- Facial flushing
- Mild reactions should be treated by slowing the intravenous infusion so that it is administered over 60 minutes.

Moderate reactions to Desmopressin should be treated as follows:

- Discontinue Desmopressin
- Assess the patient
- All reactions should be reported as per local hospital reaction policy and should be managed in accordance with the guidance from the National Immunisation Advisory Committee (NIAC,2023).

Severe allergic reactions to Desmopressin should be managed in accordance with the guidance fromthe National Immunisation Advisory Committee (NIAC,2023).

Platelet or Plasma Transfusion

Anaphylactic reactions to platelet or plasma transfusion should be managed in accordance with the guidance from theNational Immunisation Advisory Committee (NIAC,2023)

Initiate 'PRICE' as supportive care for all joint bleeds

- **Protection:** Reduce weight bearing or stress on the affected joint or muscle by providing crutches or other supports such as a 'collar and cuff' for the arm. Avoid putting weight on the affected side completely for the first 48 hours; and possibly longer if it is a severe bleed.

- **Rest:** The affected arm or leg should be gently placed on a pillow or in a sling or bandage. The individual should not move the bleeding joint.

- **Ice**: Wrap an ice pack in a damp towel and place over bleed. After 5 minutes, remove ice for 10 minutes. Repeat this step for as long as the joint feels hot. This may help decrease pain and bleeding.

- **Compression:** Gentle pressure from a tensor bandage (e.g. Tubigrip, size appropriate for the patient's limb) can help to limit bleeding and support the joint. Use compression carefully with muscle bleeds if a nerve injury is suspected.

- **Elevation:** Raise the affected area above the heart. This may slow blood loss by lowering pressure in the area of the bleed.

Ensure that the patient is referred to a physiotherapist for assessment and treatment.

Surgical Management of the Patient with a Bleeding Disorder

- Patients with bleeding disorders should ideally have surgery in a hospital where there is a Haemophilia Comprehensive Care Centre and haemostatic management should be supervised by the CCC Team
- In rare circumstances surgery may need to be performed in a hospital without a CCC, such as in emergencies or where the person needs to avail of specialist surgical services.
- In these circumstances, haemostatic management must be determined by the patient's CCC and it is recommended that the local Haematology service provides on-site consultation

In the event that a person with a bleeding disorder is undergoing surgery in a non-specialist CCC, the clinical staff should ensure the following steps are undertaken:

Pre- Operative Care

- Confirm the patient's known bleeding diagnosis, baseline levels, inhibitor status and treatment of choice with the patient and the relevant CCC.
- Confirm the patient's virology (i.e., Hepatitis A, B, C and HIV) and TSE at-risk status withthe CCC.
- For patients registered with the National Coagulation Centre, a procedure treatment plan can be requested by completing the form available at https://www.stjames.ie/services/hope/nationalcoagulationcentre/ The form is located under the section titled **'Patient having a procedure'**. Once completed, please return the request to the National Coagulation Centre via email at NCC@stjames.ie
- Liaise with local Blood Transfusion Laboratory to ensure availability of adequate clotting factor concentrate.
- Ensure a 'No NSAIDS, No Aspirin, No Heparin and No IM injections' note is communicated and recorded clearly in the drug idiosyncrasies section of the patient's prescription form, and in all other relevant healthcare records e.g., Nursing Care Plans etc. **The only NSAIDS that are allowed for patients with bleeding disorders are Etoricoxib and other selective COX2 inhibitors.**
- Ensure that the local Anaesthetic Department / Team are informed that epidural and spinal anaesthesia are generally contra-indicated in patients with bleeding disorders. Discuss with Consultant Haematologist at the CCC if Neuraxial anaesthesia is being considered. This must be clearly documented in the patient's healthcare record.

Post- Operative Care

- Liaise with the relevant CCC to determine the requirement for ongoing haemostatic treatment and factor levels.
- Ensure there are adequate supplies of the CFC in the blood transfusion laboratory to cover ongoing CFC requirements.
- Ensure that the patient is provided with adequate haemostatic cover for all invasive procedures e.g., placement of central lines or removal of sutures, clips, drains etc.
- As these procedures are likely to occur some days after the surgery the patient's CCC should be contacted to advise regarding additional treatment requirements.

Pregnancy Management

- Women who are carriers of FVIII or FIX deficiency or who have a factor deficiency or other bleeding disorder should have an individual management plan for labour and delivery determined collaboratively by the woman, her CCC and the woman's Obstetrician.
- This plan should be made available to the woman, the obstetrical department /provider, the local Haematologist, the Paediatric Haematologist in the relevant CCC and the woman's GP.
- For carriers of FVIII or FIX deficiency, it is recommended that the foetal sex is determined by ultrasound from 18 weeks onwards.
- The CCC should be informed of the sex of the foetus. Foetal sexing is not necessary if the bleeding disorder is not an X-linked disorder.
- Significant proportions of carriers for FVIII or FIX deficiency have low personal factor levels and may need haemostatic treatment peripartum. This will be determined by the woman's CCC.
- The woman's obstetrical department/provider should liaise with their local Blood Transfusion Laboratory to ensure availability of adequate clotting factor concentrate, if indicated.
- The woman's obstetrical department/provider should liaise with the local haematology laboratory and /or the haematology laboratory at Children's Health Ireland at Crumlin or laboratory at CUH if testing of maternal and or neonatal factor levels is anticipated.

Maternal labour, delivery and postpartum period management

- Patients with low factor levels or a bleeding disorder which does not correct in pregnancy may require haemostatic treatment at the time of delivery.
- The CCC should be contacted to advise on the appropriate treatment, dose and required blood testing.

Neuraxial Anaesthesia

- The use of epidural or spinal anaesthesia is contra-indicated in patients with factor levels less than the laboratory lower limit of the reference range in the third trimester or in patients whose bleeding disorder does not correct in pregnancy.
- Patients with confirmed normal factor levels in the third trimester may receive epidural or spinal anaesthesia if required. In all other cases discuss with the Consultant Haematologist at the CCC.

Analgesia

- The use of Intramuscular injections e.g., Pethidine are contra-indicated in women with low factor levels or a bleeding disorder which does not correct in pregnancy.
- Alternative analgesia such as inhaled nitrous oxide and oxygen or intravenous Remifentanil is acceptable for patients with low factor levels or a bleeding disorder which does not correct in pregnancy.
- For women with low factor levels or a bleeding disorder which does not correct in pregnancy, appropriate options for analgesia MUST be discussed with the local Maternity unit Anaesthetic service in advance.

Post- Partum Management

- Normal factor levels should be maintained for 3-5 days following vaginal delivery and for 5-7 days after caesarean section.
- In the event the patient with a factor deficiency has received factor replacement to cover the delivery, it will be necessary to send factor levels daily for at least 3 days following vaginal delivery and for at least 5 days following caesarean section.
- Postpartum, factor levels (in particular FVIII and VWF) can fall quickly in women who have low baseline levels but who have had a pregnancy-induced rise in levels and therefore have not needed treatment for labour.
- If a patient with a factor deficiency has excessive bleeding post-partum, factor levels should be sent and advice obtained from the CCC in addition to usual obstetrical management.
- Delayed post-partum haemorrhage is a feature of inherited bleeding disorders and affected women should be provided with emergency contact numbers for their CCC and Obstetric Unit / Provider following discharge.

Management of the infant during labour and delivery

Please note: The following options are for guidance only as individual delivery plans may vary and the formal delivery plan should be followed in each case.

Severe or moderately severe haemophilia

Options will depend on the gender of the foetus (if known) and whether the foetus is confirmed as affected.

Option 1 - Fetal sex assigned as male but Haemophilia status unknown

The fetal sex is assigned as male by ultrasound or maternal blood sampling but Haemophilia status unknown:

- There should be a lower threshold to caesarean section due to the need to avoid instrumental delivery. However, the final decision for mode of delivery needs to take into account other obstetric factors, as appropriate. This decision should be made at a senior level, ideally with multidisciplinary involvement.
- Ventouse delivery and/or mid-cavity rotational forceps should be avoided. Lift out forceps can be performed if deemed necessary by the Consultant Obstetrician.
- If an instrumental delivery is performed, there should be urgent analysis of a cord blood sample for foetal factor level (see below), an urgent cranial ultrasound and urgent referral to the Paediatric Haematology service in Children's Health Ireland at Crumlin/CUH.
- Foetal scalp blood sampling and scalp electrodes should be avoided, where possible.
- Factor levels should be measured on a cord blood sample. If the child has had a Ventouse or forceps delivery the factor level should be processed as an emergency. Please send cord blood in a 2.5 mls citrate tube via your laboratory to the laboratory at Children's Health Ireland at Crumlin/CUH.

Please document the sex of baby and the specific factor deficiency on the request form.

- Cranial ultrasound should be performed after an instrumental delivery and prior to discharge in all neonates with confirmed severe or moderate haemophilia.

Note that cranial ultrasound has a low sensitivity for subdural bleeds and if there is clinical suspicion, consideration should be given to MRI or CT imaging.

- Vitamin K should be administered by the oral and not the intramuscular route, in the absence of a documented normal factor level.
- Intramuscular injections should be avoided in infants with haemophilia.
- Routine vaccinations including BCG can be administered without haemostatic support.
- Heel prick can be performed for Guthrie card analysis without haemostatic support.

- If the factor level is reduced or there are any concerns regarding bleeding, the Paediatric Haematologist on–call at Children's Health Ireland at Crumlin/CUH should be contacted immediately.

Option 2- Confirmed affected male

The fetus is confirmed as an affected male by amniocentesis and genetic testing:

- Foetal scalp electrodes and foetal capillary sampling should be avoided, where possible.
- Instrumental delivery should be avoided, where possible. In the event that an instrumental delivery is performed, an urgent factor level (see below) and an urgent Cranial Ultrasound should be performed.

Note that cranial ultrasound has a low sensitivity for subdural bleeds and if there is clinical suspicion, consideration should be given to MRI or CT imaging.

- Factor levels should be measured on a cord blood sample. If the child has had a Ventouse or forceps delivery the factor level should be processed as an emergency. Please send cord blood in a 2.5 mls citrate tube via your laboratory to the laboratory at Children's Health Ireland at Crumlin/CUH. Please document the sex of baby and the specific factor deficiency on the request form.
- Vitamin K should be administered by the oral and not the intramuscular route.
- Intramuscular injections should be avoided in infants with haemophilia.
- Routine vaccinations including BCG can be administered without haemostatic support.
- The Heel prick can be performed for Guthrie card analysis without haemostatic support.
- The Paediatric Haematologist on–call at Children's Health Ireland at Crumlin/CUH shouldbe contacted regarding neonatal management.

Option 3- Fetal sex assigned as female but Haemophilia carrier status unknown

- The fetal sex is assigned as female by ultrasound or maternal blood sampling but Haemophilia carrier status is unknown:
- There is no restriction on the use of fetal scalp electrodes or fetal capillary sampling or instrumental delivery if clinically indicated.

However, since a small number of female carriers of haemophilia have low factor levels, there is apotential risk of bleeding complications after such procedures.

- Prompt analysis of cord blood factor levels and clinical awareness are therefore recommended.
- Factor levels should be measured on a cord blood sample. If the child has had a Ventouse or forceps delivery the factor level should be processed as an emergency. Please send cord blood in a 2.5 mls citrate tube via your laboratory to the laboratory at Children's Health Ireland at Crumlin or the laboratory at CUH.

Please document the sex of baby and the specific factor deficiency on the request form.

- Cranial ultrasound should be performed after an instrumental delivery in female neonateswith low factor levels.

Note that cranial ultrasound has a low sensitivity for subdural bleeds and if there is clinical suspicion, consideration should be given to MRI or CT imaging.

- Vitamin K may be given by intramuscular injection.
- The heel prick test and routine vaccinations may be given without haemostatic support.
- The neonate should be referred to the Paediatric Haematology service in Children's Health Ireland at Crumlin or to the Paediatric Haematologist in CUH, even if initial factor levels are normal.

Severe bleeding disorder other than FVIII or FIX deficiency

- There should be a lower threshold to caesarean section due to the need to avoid instrumental delivery.
- Ventouse delivery and/or mid-cavity rotational forceps should be avoided. Lift out forceps can be performed if deemed necessary by the Consultant Obstetrician.
- If an instrumental delivery is performed, there should be urgent analysis of a cord blood sample for fetal factor level (see below if applicable), an urgent cranial ultrasound and urgent referral to the Paediatric Haematology service in Children's Health Ireland at Crumlin /CUH.
- Foetal scalp blood sampling and scalp electrodes should be avoided, where possible.
- Factor levels should be measured on a cord blood sample. (In some cases, no cord blood haemostatic testing is indicated for this bleeding disorder). If the child has had a Ventouseor forceps delivery the factor level should be processed as an emergency. Please send cord blood in a 2.5 mls citrate tube via your laboratory to the laboratory at Children's Health Ireland at Crumlin/CUH. Please document the sex of baby and the specific factor deficiency on the request form.
- Vitamin K should be administered by the oral and not the intramuscular route.
- Intramuscular injections should be avoided.
- Routine vaccinations including BCG can be administered without haemostatic support.
- The Heel prick can be performed for Guthrie card analysis without haemostatic support.
- If the factor level is reduced or there are any concerns regarding bleeding, the Paediatric Haematologist on–call at Children's Health Ireland at Crumlin/CUH should be contacted immediately.
- The neonate should be referred to Paediatric Haematology in Children's Health Ireland at Crumlin/CUH for out-patient follow up.

Mild Haemophilia and Mild Bleeding Disorders

There is no restriction on the use of foetal scalp electrodes or foetal capillary sampling or instrumental delivery if clinically indicated. However, there is a potential risk of bleeding complications after such procedures.

- Prompt analysis of cord blood factor levels (if applicable) and clinical awareness ofbleeding are therefore recommended.
- If bleeding is suspected, there should be an urgent referral to Paediatric Haematology atChildren's Health Ireland at Crumlin/CUH.
- The factor level (if applicable, the delivery plan for some bleeding disorders will specifythat no cord blood testing will be required) will should be measured on a cord blood sample.
- If the child has had a Ventouse or forceps delivery the factor level should be processed asan emergency. Please send cord blood in a 2.5 mls citrate tube via your laboratory to the laboratory at Children's Health Ireland at Crumlin/CUH. Please document the sex of baby and the specific factor deficiency on the request form.
- Vitamin K may be given by intramuscular injection.
- The heel prick test and routine vaccinations may be given without haemostatic support.
- The neonate should be referred to the Paediatric Haematology service in Children'sHealth Ireland at Crumlin/CUH.

References

https://wfh.org/

https://www.hpra.ie/

https://www.hiqa.ie/reports-and-publications/niac-immunisation-guideline/anaphylaxis

https://www.medicines.ie/medicines/fibryga-1-g-powder-and-solvent-for-solution-for-injection-infusion-35009/doc-history

Appendices

Appendix 1: Quick reference 3- How to calculate an initial dose of clotting factor concentrate

NB: Treatment plans for patients with bleeding disorders must be agreed with the patient's comprehensive care centre and with the local Haematology service.

Factor VIII/Factor IX/VWD

You need to know:

- The patient's weight in kilograms
- The patient's baseline clotting factor level in % (where 100% = 1.0 IU/ml, 50% = 0.5 IU/ml, 5% = 0.05 IU/ml)
- The site and severity of the bleed (to determine the factor rise needed – see chapters 1-3)
- Any history of inhibitors

Calculation:

- Rise required = desired level of factor concentrate (%) minus baseline factor level (%)
- Dose required in units = [Rise Required (%) multiplied by Weight(kg)] divided by the K factor
- K factor is different for different factor concentrates:

Factor Concentrate	**K factor**
Factor VIII Products	
Altuvoct (FVIII)	2
Elocta (FVIII)	2
Factor IX Products	
Alprolix (FIX)	1
Von Willebrand Products	
Wilate (FVIII and VWF)	2
Veyvondi (VWF)	2

Bypassing Agents

Bypassing agents: FEIBA and Recombinant factor VIIa (Novoseven) are dosed by weight.

Feiba	50-80 units/kg as a bolus. Maximum dose 200units/kg in 24 hours
NovoSeven	90 micrograms/kg, repeated 2-4 hourly (except for FVII deficiency, see below)

Rare bleeding disorders

NB Factor replacement treatment may not be required in all cases (see Chapter 7).

Factor deficiency	**Factor replacement**	**Initial dose**
Fibrinogen	Fibrinogen concentrate (Fibryga)	50-100mg/kg
Factor II	Prothrombin complex concentrate	20-40 IU/kg
Factor V	SD frozen plasma (Octaplas)	15-25 mls/kg
Factor VII	Recombinant factor VIIa (NovoSeven)	15-30 micrograms/kg
Factor X	Coagadex	25 IU/kg
Factor XI	SD frozen plasma (Octaplas)and Tranexamic acid	15-25 mls/kg 15-20 mg/kg PO QDS
FXIII	Fibrogammin	10-40 IU/kg

Appendix 2: Quick Reference 4 -Administration information on Clotting Factor Concentrates

Note: Please follow hospital policy for the prescription of Clotting Factor Concentrates.
The person administering the concentrate is responsible for recording the batch numbers and the indication for treatment.

Name	Presentation	Solvent Volume	Used for	Administration Instructions
ALTUVOCT Recombinant FVIII	250 units 500 units 1000 units 2000 units 3000 units 4000 units	All vials are 3 ml	Factor VIII Deficiency	▪ Slow Intravenous Bolus at a max rate of 10mls per min. ▪ Can be administered once daily ▪ Once reconstituted use immediately ▪ Do not place reconstituted solution back in refrigerator. ▪ Pre-filled glass syringes are not compatible with clave connectors,therefore if administering Elocta via a clave connector, PICC line or CVAD you should draw the reconstituted solution into a plastic syringe prior to administration.
ELOCTA Recombinant FVIII	250 units 500 units 1000 units 1500 units 2000 units 3000 units	All vials are3 ml	Factor VIII Deficiency	▪ Slow Intravenous Bolus at a max rate of 10mls per min. ▪ Can be administered once or twice daily. ▪ Once reconstituted use immediately or within 6 hours up to 30 ^{0} C. ▪ Do not place reconstituted solution back in refrigerator. ▪ Pre-filled glass syringes are not compatible with clave connectors,therefore if administering Elocta via a clave connector, PICC line or CVAD you should draw the reconstituted solution into a plastic syringe prior to administration.

ALPROLIX Recombinant FIX	250 units 500 units 1000 units 2000 units 3000 units	All vials are5 ml	Factor IX Deficiency	▪ Slow Intravenous Bolus at a max rate of 10mls per min. ▪ Can be administered once daily as bolus. ▪ Once reconstituted use immediately or within 6 hours up to 30 ^{0} C ▪ Do not place reconstituted solution back in refrigerator. ▪ Pre filled glass syringes are not compatible with clave connectors, therefore if administering Alprolix via a clave connector, PICC line or CVAD you should draw the reconstituted solution into a plastic syringe prior to administration.
NOVOSEVEN Recombinant FVIIa	1mg (50kiu) 2mg (100kiu) 5mg (250kiu)	1 ml 2 ml 5 ml	Factor VII Deficiency. FVIII & FIX deficient patients with inhibitors.	▪ Slow Intravenous Bolus at a rate not exceeding 5mls per min. ▪ Once reconstituted, administer immediately or within 6 hours up to 25 ^{0} C ▪ NovoSeven should be prescribed in Milligrams only. ▪ Pre-filled glass syringes are not compatible with clave connectors, therefore, if administering NovoSeven via a clave connector, PICC line or CVAD you should draw the reconstituted solution in to a plastic syringe prior to administration.
FEIBA Factor Eight Inhibitor Bypassing Agent. Plasma derived	500 units 1000 units 2500 units	5ml 10ml 20ml	FVIII & FIX deficient patients with inhibitors.	▪ Slow Intravenous Bolus at a rate of 10iu/kg per minute. ▪ Once reconstituted administer immediately or within 3 hours up to 25 ^{0} C. ▪ Do not place reconstituted solution back in refrigerator.
WILATE FVIII & VWF Plasma derived	500 units 1000 units	5 ml 10 ml	Von Willebrand Disease not responsive to Desmopressin.	▪ Slow Intravenous Bolus at a rate not exceeding 3mls per minute. ▪ Once reconstituted administer immediately or within 4 hours up to 25 ^{0} C. ▪ Do not place reconstituted solution back in refrigerator.

FIBROGAMMIN FXIII Concentrate Plasmaderived	250 units 1250 units	4ml 20 ml	FXIII Deficiency	▪ Slow Intravenous Bolus at a rate not exceeding 4mls per minute. ▪ Once reconstituted administer immediately
COAGADEX Plasma Derived		2.5 ml	FX Deficiency	▪ Slow Intravenous Bolus at a rate not exceeding 10mls per minute. ▪ Once reconstituted use immediately or within 1hour up to 25 ^{0}C.
Factor X	250 units 500 units	5 ml		▪ Do not place reconstituted solution back in refrigerator.
FIBRYGA Fibrinogen Concentrate Plasma Derived		50 ml	Fibrinogen Deficiency	▪ Reconstitute each 1g with 50mls Water for Injection ▪ Slow Intravenous Bolus or infusion drip at a rate of 5mls – 10mls perminute. ▪ Once reconstituted use immediately or within 24 hours up to 25 ^{0}C. ▪ Do not place reconstituted solution back in refrigerator.
VEYVONDI Recombinant VWF	650 units 1300 units	5 ml 10 ml	Adults (age 18 years & over) with Von Willebrand Disease not response to DDAVP	• Slow intravenous bolus at a max rate of 4mls per minute • Once reconstituted use immediately or within 3 hours (up to 25 Celsius) • Do not place the reconstituted solution back in refrigerator • It is important to allow the reconstituted solution to stand for 5 minutes while the two vials are still connected. The vials should then be gently swirled to ensure the powder is completely dissolved before drawing thesolution in to a plastic syringe • It is not uncommon for a few flakes or particles to remain in the product vial after reconstitution. The filter within the Mix2Vial device will preventthe particles from transferring to the syringe. You should not use the product if the solution in the syringe appears cloudy or contains flakes orparticles after filtration ▪ If you need to co-administer rFVIII, the rFVIII should be administeredwithin 10 minutes of the infusion of Veyvondi being administered

The SPC details and the reconstitution guidelines can be found by searching for the medicine either via HPRA www.hpra.ie (find a medicine) or via EMA https://www.ema.europa.eu/en/medicines . At the time of use please read all instructions for the reconstitution and administration which are included in the product box. The tamperproof label of the CFC boxes should not be opened for instructions unless the product is going to be used. As already outlined above and guidance on the reconstitution of CFC can be found via HPRA or EMA websites.