# Adults with Haemophilia and Related Bleeding Disorders

## Acute Treatment Guidelines

**Adult Comprehensive Care Centres (CCC) Ireland:**

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<td>The National Coagulation Centre (NCC),</td>
<td>(01) 4162141</td>
</tr>
<tr>
<td>St. James’s Hospital, Dublin 8.</td>
<td></td>
</tr>
<tr>
<td>Cork Coagulation Centre,</td>
<td>(021) 4922278</td>
</tr>
<tr>
<td>Cork University Hospital, Wilton, Cork City</td>
<td></td>
</tr>
<tr>
<td>Haemophilia Treatment Centre,</td>
<td>(091) 524222</td>
</tr>
<tr>
<td>University Hospital Galway, Newcastle Road,</td>
<td></td>
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<tr>
<td>Galway.</td>
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In order to avoid repetition, the following were placed into separate chapters: Pregnancy management, Management of the neonate, Surgical management, Supportive care of joint bleeds and allergic reactions to CFCs.

The dosage formula for Elocta and Alprolix have been taken from the appendices and put into the body of text of the relevant chapters.

Management of FVIII and FIX patients with inhibitors added to the body of the text of the relevant chapters.

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
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1.0 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 evidence-based guidelines 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)

Due to the complexity of haemophilia and its treatment, care of persons with these bleeding disorders should be co-ordinated 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
- Cork Coagulation Centre, Cork University Hospital.
- Paediatric CCC - Children’s Health Ireland, Crumlin – All persons <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 in collaboration with the patient’s CCC. Accordingly, the NHC has commissioned these guidelines 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.
1.1 Key Statements

- Acute treatment of all persons with an inherited bleeding disorder should be co-ordinated by the CCC with which the patient is registered. These guidelines 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. Elocta 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. DDAVP 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 guidelines.

1.2 Scope

These Guidelines apply 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 Willebrand’s Disease
- Rare bleeding disorders (inherited deficiencies of factors I (Fibrinogen), II, V, VII, X, XI, XIII)
- Inherited disorders of Platelet function

1.3 Definitions/Glossary

Throughout this document the following abbreviations / acronyms are used:

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<th>Abbreviation</th>
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<tr>
<td>VWD</td>
<td>Von Willebrand Disease</td>
</tr>
<tr>
<td>VWF</td>
<td>Von Willebrand Factor</td>
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<tr>
<td>CCC</td>
<td>Comprehensive Care Centre</td>
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<tr>
<td>CFC</td>
<td>Clotting Factor Concentrates and other biological products</td>
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<td>BPAs</td>
<td>Bypassing agents</td>
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<tr>
<td>RCo</td>
<td>Ristocetin Cofactor Activity</td>
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<td>CUH</td>
<td>Cork University Hospital</td>
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<td>SJH</td>
<td>St James’s Hospital</td>
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<tr>
<td>CVAD</td>
<td>Central Venous Access Device</td>
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<td>PICC</td>
<td>Peripherally Inserted Central Catheters</td>
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<td>CBA</td>
<td>Collagen binding assays</td>
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2.0 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.
- 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.

2.1 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 **www.hpra.ie/Medicines/findamedicine**
3.0 Factor VIII Deficiency (Haemophilia A)

3.1 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.

3.2 Severity

Severity relates to the baseline level of factor VIII.

<table>
<thead>
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<th>Factor VIII Activity Level</th>
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<td>Severe disease</td>
<td>&lt;1% (&lt;0.01 IU/ml)</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>1–5% (0.01-0.05 IU/ml)</td>
</tr>
<tr>
<td>Mild disease</td>
<td>&gt;5% (&gt;0.05 IU/ml)</td>
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Table 1.0: Factor VIII Deficiency Severity Categories

3.3 Treatment Administration

- Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. Elocta for FVIII deficiency
- 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. DDAVP 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. Elocta, DDAVP®/Desmopressin Injection and/or Tranexamic Acid. Clotting Factor Concentrates for acute treatment are held in the Blood Transfusion department of each hospital.

3.4 Clotting Factor Concentrate – Elocta

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

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

Elocta comes as a powder and solvent in a pre-filled syringe that must be reconstituted for solution. It is administered as a bolus infusion.
3.4.1 Dose Calculation- Elocta

Bolus Dosing in FVIII Deficiency CFC i.e. 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)

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

\( \text{K factor for FVIII} = 2 \)

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

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 Elocta via a clave connector, PICC line or CVAD the reconstituted solution should be drawn into a plastic syringe prior to administration.
### 3.4.2 Administration- Elocta

- Elocta should be administered as a slow intravenous push at a rate not exceeding 10mls 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.

### 3.5 DDAVP/ Desmopressin

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

DDAVP® 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.

#### 3.5.1 Dose Calculation- DDAVP/ Desmopressin

DDAVP is administered intravenously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.

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

#### 3.5.2 Dose Administration- DDAVP/ Desmopressin

DDAVP comes in 1ml ampoule which contains Desmopressin acetate 4 micrograms per ml in a sterile, aqueous solution for injection.

DDVAP should be added to 100mls of normal saline using an aseptic technique.

The 100ml solution should be administered intravenously over 30-60 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 100mls of normal saline and this will be administered IV over 30-60 minutes.

#### 3.5.3 Contraindications/Cautions- DDAVP/ Desmopressin

**DDAVP 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

- DDAVP should only be administered under the supervision of a specialist with appropriate laboratory 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 DDAVP infusion.
- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia. Treatment with DDAVP 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, DDAVP/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 DDAVP/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 DDAVP/Desmopressin Injection in elderly patents and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice DDAVP 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 DDAVP/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).
3.6 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.

3.6.1 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

3.6.2 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.

3.6.3 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).

3.7 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 who 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

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is inhibitor present currently or in past history?</td>
<td></td>
</tr>
<tr>
<td>What is patient’s current treatment of choice?</td>
<td></td>
</tr>
<tr>
<td>Has patient ever received Immune tolerance treatment? If yes, when was this given and did the patient achieve eradication of the inhibitor?</td>
<td></td>
</tr>
</tbody>
</table>

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

#### 3.7.1 Treatment Options for Factor VIII patients with inhibitors

##### 3.7.1.1 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.

##### 3.7.1.2 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).

### 3.7.1.3 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.*

<table>
<thead>
<tr>
<th>BPA</th>
<th>Initial dose</th>
<th>Subsequent dose and frequency</th>
<th>Important Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feiba</td>
<td>50-80 units/kg</td>
<td>50 units/kg every 8-12 hours</td>
<td>DO NOT EXCEED a total dose of 200 units/kg in a 24 hour period</td>
</tr>
<tr>
<td>NovoSeven</td>
<td>90 micrograms/kg</td>
<td>90 micrograms/kg every 2-4 hours</td>
<td></td>
</tr>
</tbody>
</table>

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

### 3.7.1.4 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)

### 3.7.2 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.
Factor VIII Deficiency (Haemophilia A)

- Hemlibra CANNOT be used to treat an acute bleed and a BPA 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.

### 3.7.2.1 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.

### 3.7.2.2 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.

### 3.7.2.3 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.
4.0 Factor IX Deficiency (Haemophilia B)

4.1 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.

4.2 Severity

Severity relates to the baseline level of factor IX.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Factor IX Activity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe disease</td>
<td>&lt;1% (&lt;0.01 IU/ml)</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>1–5% (0.01-0.05 IU/ml)</td>
</tr>
<tr>
<td>Mild disease</td>
<td>&gt;5% (&gt;0.05 IU/ml)</td>
</tr>
</tbody>
</table>

Table 5: Factor IX Severity Categories

4.3 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 of each hospital.

4.3.1 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.
4.3.1.1 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**

\[
\text{Rise required} = \text{desired level of factor concentrate (%) minus baseline factor level (%)}
\]

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

Dose required = Rise required (%) \times Weight (kgs)

\[
K
\]

**K factor for FIX = 1**

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

*Table 6: Desired Initial Post Treatment Factor Levels for Bleeds Types in Persons with FIX deficiency*
4.3.1.2 Dose Administration- Alprolix

Alprolix should be:

- administered as a slow intravenous push over 5 minutes.
- a sample for 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.

4.3.2 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.

4.3.2.1 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

4.3.2.2 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.

4.3.2.3 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 VIIIa (risk of thrombosis).

### 4.4 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 who have a current or past history of inhibitors.
Factor IX Deficiency (Haemophilia B)

- 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).

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

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

### 4.4.1 Treatment options for patients with Factor IX patients with inhibitors

#### 4.4.1.1 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.

#### 4.4.1.2 Cautions with Bypassing Agents in patients with Factor IX inhibitors

- Arterial and venous thrombotic complications have been reported during and after treatment with BPAs.
Factor IX Deficiency (Haemophilia B)

- 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.

4.4.1.3 Dose Calculation of Bypassing Agents in patients with Factor IX inhibitors

<table>
<thead>
<tr>
<th>BPA</th>
<th>Initial dose</th>
<th>Subsequent dose and frequency</th>
<th>Important Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feiba</td>
<td>50-80 units/kg</td>
<td>50 units/kg every 8-12 hours</td>
<td>DO NOT EXCEED a total dose of 200 units/kg in a 24 hour period</td>
</tr>
<tr>
<td>Novoseven</td>
<td>90 micrograms/kg</td>
<td>90 micrograms/kg every 2-4 hours</td>
<td></td>
</tr>
</tbody>
</table>

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

4.5 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)
5.0 Von Willebrand Disease (VWD)

5.1 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 Ristocetin Cofactor Activity (RCo) 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 RCo or CBA assays are lower than the VWF antigen in types 2A, 2B and 2M.
  
  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.
5.2 Severity

The severity relates to the VWF level and activity.

<table>
<thead>
<tr>
<th>VWF antigen and/or activity</th>
<th>Clinical bleeding phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low VWF 0.3-0.5 IU/ml</td>
<td>Some patients may bleed with invasive procedures, or have menorrhagia or mucocutaneous bleeding</td>
</tr>
<tr>
<td>Type 1 &lt;0.3 IU/ml</td>
<td>Bleeding after invasive dental or surgical procedures, menorrhagia, mucocutaneous bleeding</td>
</tr>
<tr>
<td>Type 2 &lt;0.3 IU/ml (RC or CBA)</td>
<td>Ratio of activity to antigen &lt;0.5-0.7</td>
</tr>
<tr>
<td>Type 3 Levels are very low or undetectable</td>
<td>Mucocutaneous bleeding, menorrhagia, post-operative bleeding. May have haemarthrosis, muscle haematomas</td>
</tr>
</tbody>
</table>

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

5.3 Treatment Administration

- Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. Wilate 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. DDAVP 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, DDAVP 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 DDAVP. The CCC will advise on the appropriate treatment to use.
- The Clinician should establish the treatment of choice i.e. Wilate, DDAVP®/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:

**5.3.1 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)

### 5.3.1.1 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 in Mix2Vial™.

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

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

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

Dose required = \( \frac{\text{Rise Required} \times \text{Weight (kgs)}}{\text{K factor for Wilate calculation}} \)

K factor for Wilate calculation = 2

100% (1.0 IU/ml) – 12 % (<0.12 IU/ml) x 50kg = 4400 units

Example:

A 50kg patient with a level <0.12 IU/ml (12%) who needs a post level of 1.0 IU/ml (100%) will require 4400 units concentrate. Round to up to the nearest available vial size= 4500 units.

### 5.3.1.2 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.
5.3.2 DDAVP/ Desmopressin

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

DDAVP® 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.

5.3.2.1 Dose Calculation- DDAVP/ Desmopressin

DDAVP is administered intravenously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.

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

5.3.2.2 Dose Administration- DDAVP/ Desmopressin

DDAVP comes in 1ml ampoule which contains Desmopressin acetate 4 micrograms per ml in a sterile, aqueous solution for injection. DDVAP should be added to 100mls of normal saline using an aseptic technique. The 100ml solution should be administered intravenously over 30-60 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 100mls of normal saline and this will be administered IV over 30-60 minutes.

5.3.2.3 Contraindications/Cautions- DDAVP/ Desmopressin

**DDAVP 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 Willebrand's 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**

- DDAVP should only be administered under the supervision of a specialist with appropriate laboratory 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
Von Willebrand Disease (VWD)

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 DDAVP infusion.

- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia. Treatment with DDAVP 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, DDAVP/Desmopressin Injection should be administered after confirmation of normal baseline sodium.

- When repeated doses are used to control bleeding in haemophilia or von Willebrand’s 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 DDAVP/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 DDAVP/Desmopressin injection in elderly patents and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice DDAVP is not usually recommended for patients > 55 years.

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 DDAVP/Desmopressin Injection.

- Precautions must be taken in patients at risk for increased intracranial pressure.

- Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50ml/min)

5.3.3 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.
5.3.3.1 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

5.3.3.2 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.

5.3.3.3 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.
Von Willebrand Disease (VWD)

- 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).
6.0 Platelet Function Disorders

6.1 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’s Thrombasthenia 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.

6.2 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. Glanzmanns thrombasthenia or Bernard Soulier syndrome.
- The patient’s CCC will be able to advise on the bleeding severity for individual patients.

6.3 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
- DDAVP
- 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. DDAVP 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:
### 6.3.1 Platelet Transfusion

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

### 6.3.2 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.

#### 6.3.2.1 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.

#### 6.3.2.2 Dose Administration- Recombinant Factor VIIa/NovoSeven

- Recombinant Factor VIIa / NovoSeven comes 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.
### 6.3.3 DDAVP/ Desmopressin

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

DDAVP® 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.

#### 6.3.3.1 Dose Calculation- DDAVP/ Desmopressin

DDAVP is administered intravenously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.  
**Example:** A 60kg patient requiring DDAVP, the dose should be calculated as 60 kg x 0.3 micrograms = 18 micrograms.

#### 6.3.3.2 Dose Administration- DDAVP/ Desmopressin

DDAVP comes in 1ml ampoule which contains Desmopressin acetate 4 micrograms per ml in a sterile, aqueous solution for injection.  
DDVAP should be added to 100mls of normal saline using an aseptic technique. The 100ml solution should be administered intravenously over 30-60 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 100mls of normal saline and this will be administered IV over 30-60 minutes.

#### 6.3.3.3 Contraindications/Cautions- DDAVP/ Desmopressin

**DDAVP 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**
- DDAVP should only be administered under the supervision of a specialist with appropriate laboratory 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 DDAVP infusion.
Platelet Function Disorders (PFDs)

- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia. Treatment with DDAVP 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, DDAVP/Desmopressin Injection should be administered after confirmation of normal baseline sodium.
- When repeated doses are used to control bleeding in haemophilia or von Willebrand’s 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 DDAVP/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 DDAVP/Desmopressin injection in elderly patients and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice DDAVP is not usually recommended for patients > 55 years.

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 DDAVP/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).

6.3.4 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.
6.3.4.1 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

6.3.4.2 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.

6.3.4.3 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
Platelet Function Disorders (PFDs)

- 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).
7.0 Rare Bleeding Disorders

7.1 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.

7.2 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.

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

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

7.3 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.
Rare Bleeding Disorders (RBDs)

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

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Factor Replacement Treatment (If indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>Riastap (Fibrinogen concentrate)</td>
</tr>
<tr>
<td>Factor II</td>
<td>Prothromplex (Prothrombin complex concentrate)</td>
</tr>
<tr>
<td>Factor V</td>
<td>Octaplas (Solvent detergent treated frozen plasma)</td>
</tr>
<tr>
<td>Factor VII</td>
<td>NovoSeven (Recombinant factor VIIa)</td>
</tr>
<tr>
<td>Factor X</td>
<td>Prothromplex (prothrombin complex concentrate)</td>
</tr>
<tr>
<td>Factor XI</td>
<td>FXI Concentrate or Octaplas (Solvent detergent treated frozen plasma)</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>Fibrogammin P (FXIII concentrate)</td>
</tr>
</tbody>
</table>

*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.

7.3.1 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)

7.3.1.1 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, 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.

7.3.2 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.
7.3.2.1 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

7.3.2.2 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.

7.3.2.3 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).
8.0 Bleeding Disorder of Unknown Aetiology

8.1 General Information

The diagnosis of bleeding disorder of unknown aetiology (BDUA) 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.

8.2 Severity

Severity of BDUA is variable and is determined by the patient’s clinical bleeding history.

8.3 Treatment Administration

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

- Tranexamic Acid
- DDAVP

If severe bleeding, consider random donor platelets or recombinant factor VIIa

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

8.3.1 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.

8.3.1.1 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
### 8.3.1.2 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.

### 8.3.1.3 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
- Haematura
- 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 VIIIa (risk of thrombosis).

### 8.3.2 DDAVP/ Desmopressin

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

DDAVP® 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.

#### 8.3.2.1 Dose Calculation- DDAVP/ Desmopressin

DDAVP is administered intravenously at a dose of 0.3 micrograms/kg. The maximum total dose recommended for any patient is 27 micrograms.

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

#### 8.3.2.2 Dose Administration- DDAVP/ Desmopressin

DDAVP comes in 1ml ampoule which contains Desmopressin acetate 4 micrograms per ml in a sterile, aqueous solution for injection. DDAVP should be added to 100mls of normal saline using an aseptic technique. The 100ml solution should be administered intravenously over 30-60 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 100mls of normal saline and this will be administered IV over 30-60 minutes.

#### 8.3.2.3 Contraindications/Cautions- DDAVP/ Desmopressin

**DDAVP 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

- DDAVP should only be administered under the supervision of a specialist with appropriate laboratory 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 DDAVP infusion.
- Infants, elderly and patients with serum sodium levels in the lower range of normal may have increased risk of hyponatraemia. Treatment with DDAVP 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, DDAVP/Desmopressin Injection should be administered after confirmation of normal baseline sodium.
- When repeated doses are used to control bleeding in haemophilia or von Willebrand's 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 DDAVP/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 DDAVP/Desmopressin injection in elderly patients and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease. In practice DDAVP is not usually recommended for patients > 55 years.

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 DDAVP/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).
9.0 Management of Allergic Reaction to Treatment

9.1 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 local hospital resuscitation / response protocols should be followed.

The use of the following medications is recommended:

- Adrenaline (Epinephrine) should be given by the intramuscular (IM) route at a dose of 500 micrograms (0.5mg) for example 0.5ml of 1:1000 adrenaline.
- Chlorpheniramine 10mg IV or IM and Hydrocortisone 200mg IV or IM should also be given.
- Oxygen should be administered as soon as possible (15 litres/min) using a mask with an oxygen reservoir
- Bronchodilators: Consider salbutamol (inhaled), or ipratropium (inhaled).

9.2 DDAVP/Desmopressin

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

Reactions to DDAVP

Reactions to DDAVP can be common

Mild reactions to DDAVP 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 DDAVP should be treated as follows:

- Discontinue DDAVP
- Assess the patient
- Administer Chlorpheniramine 10-20 mg IM or slow IV (over one minute)
- If required, add Hydrocortisone 100 - 200 mg IM or slow IV (over three minutes)
- If required, add Oxygen (10-12 litre/min) +/- inhaled Salbutamol (2.5mg)
- The DDAVP infusion can be restarted at a slower rate with close monitoring of the patient.
Management of Allergic Reaction to Treatment

- In the event a reaction recurs, the infusion should be stopped and the clinician should contact the relevant CCC for advice on alternative treatments.
- All reactions should be reported as per local hospital reaction policy.

Severe allergic reactions to DDAVP should be treated in accordance with local resuscitation / response protocols. The use of the following medications is recommended:

- Adrenaline (Epinephrine) should be given by the intramuscular (IM) route at a dose of 500 micrograms (0.5mg) for example 0.5ml of 1:1000 adrenaline.
- Chlorpheniramine 10mg IV or IM and Hydrocortisone 200mg IV or IM should also be given as above.
- Oxygen should be administered as soon as possible (15 litres/min) using a mask with an oxygen reservoir.
- Bronchodilators: Consider salbutamol (inhaled), or ipratropium (inhaled).
- The clinician should contact the relevant CCC for advice on alternative treatments.

9.3 Platelet or Plasma Transfusion

Adverse reactions to platelet products should be managed and reported in accordance with local hospital policy.
10.0 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.
11.0 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:

11.1 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 with the CCC.

- Obtain a written management plan from the CCC.

- 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.

- 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.
11.2 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.
12.0 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 (Crumlin) or laboratory at CUH if testing of maternal and or neonatal factor levels is anticipated.

12.1 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.

12.1.1 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.

12.1.2 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.
Pregnancy Management

- 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.

12.1.3 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.
13.0 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.

13.1 Severe or moderately severe haemophilia

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

13.1.1 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, 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, 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, Crumlin/CUH should be contacted immediately.
13.1.2 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, 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, Crumlin/CUH should be contacted regarding neonatal management.

13.1.3 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 a potential 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, 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 neonates with 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.
Management of the infant during labour and delivery

- The neonate should be referred to the Paediatric Haematology service in Children’s Health Ireland, Crumlin or to the Paediatric Haematologist in CUH, even if initial factor levels are normal.

### 13.2 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, 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 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, 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, Crumlin/CUH should be contacted immediately.
- The neonate should be referred to Paediatric Haematology in Children’s Health Ireland, Crumlin/CUH for out-patient follow up.

### 13.3 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 of bleeding are therefore recommended.
- If bleeding is suspected, there should be an urgent referral to Paediatric Haematology at Children’s Health Ireland, Crumlin/CUH.
- The factor level (if applicable, the delivery plan for some bleeding disorders will specify that no cord blood testing will be required) will 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...
Management of the infant during labour and delivery

at Children’s Health Ireland, 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’s Health Ireland, Crumlin/CUH.

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, Crumlin/CUH.
14.0 Reference List

www.wfh.org
www.hpra.ie/Medicines/findamedicine
Appendices

Appendix 1: Quick reference- 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:

<table>
<thead>
<tr>
<th>Factor Concentrate</th>
<th>K factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elocta (FVIII)</td>
<td>2</td>
</tr>
<tr>
<td>Alprolix (FIX)</td>
<td>1</td>
</tr>
<tr>
<td>Wilate (FVIII and VWF)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Bypassing Agents**

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

<table>
<thead>
<tr>
<th>Bypassing agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feiba</td>
<td>50-80 units/kg as a bolus. Maximum dose 200 units/kg in 24 hours</td>
</tr>
<tr>
<td>NovoSeven</td>
<td>90 micrograms/kg, repeated 2-4 hourly except for FVII deficiency, see below</td>
</tr>
</tbody>
</table>

**Rare bleeding disorders**

NB Factor replacement treatment may not be required in all cases – see Chapter 7

<table>
<thead>
<tr>
<th>Factor deficiency</th>
<th>Factor replacement</th>
<th>Initial dose</th>
</tr>
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<tbody>
<tr>
<td>Fibrinogen</td>
<td>Fibrinogen concentrate (Riastap)</td>
<td>50-100mg/kg</td>
</tr>
<tr>
<td>Factor II</td>
<td>Prothromplex</td>
<td>20-40 IU/kg</td>
</tr>
<tr>
<td>Factor V</td>
<td>SD frozen plasma (Octaplas)</td>
<td>15-25 mls/kg</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Recombinant factor VIIIa (NovoSeven)</td>
<td>15-30 micrograms/kg</td>
</tr>
<tr>
<td>Factor X</td>
<td>Prothromplex</td>
<td>20-30 IU/kg</td>
</tr>
<tr>
<td>Factor XI</td>
<td>FXI concentrate (NB No Tranexamic acid to be administered with FXI concentrate) Or use SD frozen plasma (Octaplas) and Tranexamic acid</td>
<td>10-15 IU/kg 15-25 mls/kg 15-20 mg/kg PO QDS</td>
</tr>
<tr>
<td>FXIII</td>
<td>Fibrogammin</td>
<td>10-40 IU/kg</td>
</tr>
</tbody>
</table>
## Appendix 2: Quick Reference - 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.

<table>
<thead>
<tr>
<th>NAME</th>
<th>PRESENTATION</th>
<th>USED FOR</th>
<th>Administration Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELOCTA</td>
<td>250 units</td>
<td>Factor VIII Deficiency</td>
<td>- Slow Intravenous Bolus at a max rate of 10mls per min.</td>
</tr>
<tr>
<td></td>
<td>500 units</td>
<td></td>
<td>- Can be administered once or twice daily.</td>
</tr>
<tr>
<td></td>
<td>1000 units</td>
<td></td>
<td>- Once reconstituted use immediately or within 3 hours.</td>
</tr>
<tr>
<td></td>
<td>1500 units</td>
<td></td>
<td>- Do not place reconstituted solution back in refrigerator.</td>
</tr>
<tr>
<td></td>
<td>2000 units</td>
<td></td>
<td>- Pre-filled glass syringes are not compatible with clave connectors,</td>
</tr>
<tr>
<td></td>
<td>3000 units</td>
<td></td>
<td>therefore if administering Elocta via a clave connector, PICC line or CVAD you should draw</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the reconstituted solution into a plastic syringe prior to administration.</td>
</tr>
<tr>
<td></td>
<td>250 units</td>
<td>Factor IX Deficiency</td>
<td>- Slow Intravenous Bolus at a max rate of 10mls per min.</td>
</tr>
<tr>
<td></td>
<td>500 units</td>
<td></td>
<td>- Can be administered once daily as bolus.</td>
</tr>
<tr>
<td></td>
<td>1000 units</td>
<td></td>
<td>- Once reconstituted use immediately or within 3 hours.</td>
</tr>
<tr>
<td></td>
<td>2000 units</td>
<td></td>
<td>- Do not place reconstituted solution back in refrigerator.</td>
</tr>
<tr>
<td></td>
<td>3000 units</td>
<td></td>
<td>- Pre-filled glass syringes are not compatible with clave connectors,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>therefore if administering Alprolix via a clave connector, PICC line or CVAD you should draw</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the reconstituted solution into a plastic syringe prior to administration.</td>
</tr>
<tr>
<td>NOVOSEVEN</td>
<td>1mg (50kiu)</td>
<td>Factor VII Deficiency</td>
<td>- Slow Intravenous Bolus at a rate of 2-5mls per min.</td>
</tr>
<tr>
<td></td>
<td>2mg (100kiu)</td>
<td></td>
<td>- Once reconstituted, administer immediately or within 24 hours once</td>
</tr>
<tr>
<td></td>
<td>5mg (250kiu)</td>
<td></td>
<td>stored between 2-8°C.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FVIII &amp; FIX deficient</td>
<td>- NovoSeven should be prescribed in Milligrams only.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients with inhibitors.</td>
<td>- Pre-filled glass syringes are not compatible with clave connectors,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>therefore if administering NovoSeven via a clave connector, PICC line or</td>
</tr>
</tbody>
</table>

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Current version of guidelines available only at www.nationalhaemophilacouncil.ie

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### Appendices

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Concentration</th>
<th>Indications</th>
<th>Administration Details</th>
</tr>
</thead>
</table>
| **FEIBA**<br>Factor Eight Inhibitor Bypassing Agent<br>Plasma derived | 500 units<br>1000 units<br>2500 units | FVIII & FIX deficient patients with inhibitors. | CVAD you should draw the reconstituted solution in to a plastic syringe prior to administration. | ▪ Slow Intravenous Bolus at a rate of 2iu/kg per minute.  
▪ Once reconstituted administer immediately or within 3 hours.  
▪ Do not place reconstituted solution back in refrigerator. |
| **WILATE**<br>FVIII & VWF<br>Plasma derived | 500 units<br>1000 units | Von Willebrand Disease not responsive to DDAVP. | ▪ Slow Intravenous Bolus at a rate not exceeding 2-3mls per minute.  
▪ Once reconstituted administer immediately or within 12 hours.  
▪ Do not place reconstituted solution back in refrigerator. |
| **FIBROGAMMIN**<br>FXIII Concentrate<br>Plasma derived | 250iu | FXIII Deficiency | ▪ Slow Intravenous Bolus at a rate not exceeding 4mls per minute.  
▪ Once reconstituted administer immediately or within 8 hours once stored between 2-8°C. |
| **PROTHROMPLEX**<br>Prothrombin Complex Concentrate<br>Plasma derived | 600 units | FX Deficiency | ▪ Slow Intravenous Bolus at a rate not exceeding 2mls per minute.  
▪ Once reconstituted use immediately or within 3 hours.  
▪ Do not place reconstituted solution back in refrigerator. |
| **FACTOR XI CONCENTRATE**<br>Plasma Derived | Individual Potency written on vial label | Factor XI Deficiency | ▪ Slow Intravenous Bolus at a rate not exceeding 3mls per minute, especially the first dose.  
▪ Once reconstituted use immediately or within 1 hour.  
▪ Do not place reconstituted solution back in refrigerator. |
| **RIASTAP**<br>Fibrinogen Concentrate<br>Plasma Derived | 1 gram | Fibrinogen Deficiency | ▪ Reconstitute each 1g with 50mls Water for Injection (not supplied with product).  
▪ Slow Intravenous Bolus or infusion drip at a rate not exceeding 5mls per minute.  
▪ Once reconstituted use immediately or within 8 hours.  
▪ Do not place reconstituted solution back in refrigerator. |
Appendices

Appendix 3: Quick Reference- Emergency treatment of patients with bleeding disorders

In Ireland, patients with bleeding disorders such as Haemophilia, Von Willebrand disease, Rare bleeding disorders and Platelet function disorders are registered with a Comprehensive Care Centre (CCC) for the treatment of these conditions. The CCCs are in St James’s Hospital and Cork University Hospital for adults (>16 years old) and in Our Lady’s Children’s Hospital, Crumlin and Cork University Hospital for children (<16 years old).

There is a Consultant Haematologist and Specialist Registrar available for advice 24/7 in the CCCs – in an emergency, contact the hospital switchboard and ask for the Haematology doctor on call: St James’s Hospital 01 4103000; Cork University Hospital 021 4546400; Our Lady’s Children’s Hospital 01 4096100.

All registered patients with bleeding disorders in Ireland should have a registration card which shows their diagnosis on the front and the contact details for their CCC on the back. If a patient attends an Emergency Department for any reason, they should be asked for their registration card (see example below).

Some patients may also present a Bleeding Disorder Alert card (see example below) which is evidence that they have a bleeding disorder and shows the contact details of the CCC they attend.

Some patients may also present a Bleeding Disorder Alert card (see example below) which is evidence that they have a bleeding disorder and shows the contact details of the CCC they attend.

If a patient does not have a registration or bleeding disorder card, they should know which CCC they attend for follow-up.

Key points for the emergency treatment of patients with bleeding disorders:

1. PHONE the patient’s CCC to confirm the diagnosis, blood levels and haemostatic treatment of choice IMMEDIATELY. The local Haematology service should also be informed as they will need to co-ordinate local treatment stocks and give local advice and support.

2. TREAT the patient before other investigations – for patients with bleeding disorders, even soft tissue injuries can result in significant bleeding so haemostatic treatment is needed as soon as possible. The CCC will advise on what haemostatic treatment to give. Standard management for bleeding should also be given e.g. transfusion of red cells if required.
Appendices

3. **Treatment available locally**: All public hospital Blood Transfusion laboratories in Ireland have one dose of the clotting factor concentrates used for Haemophilia and Von Willebrand disease, stored in the Blood Transfusion Laboratory. This will be enough to stabilise the patient and emergency stocks of clotting factor concentrates can be sent to any hospital within hours if necessary.

4. **Treatment guidelines** are available online for all of the bleeding disorders giving step-by-step guidance for managing these patients as well as help for reconstituting and administering haemostatic treatments and advice on pain management - [http://www.nationalhaemophiliacouncil.ie/home/](http://www.nationalhaemophiliacouncil.ie/home/) (see homepage picture below – tab highlighted with red oval).

![Homepage Picture](https://example.com/homepage.png)

National treatment guideline chapters are arranged by diagnosis while appendices contain information on factor administration and pain relief.

5. **Transfer** to a CCC may be arranged if necessary but only after initial haemostatic treatment has been given and the patient has been stabilised.