BACKGROUND

Coagulation factor concentrates are highly effective treatments for patients with hemostatic disorders caused by missing or defective clotting factors. Coagulation factor concentrates may be extracted from pooled donated plasma (plasma-derived) or manufactured using biotechnology (recombinant). In addition, several plasma-derived protein concentrates are available for the treatment of thrombotic disorders and hereditary angioedema.

These factor concentrates available to Canadian patients, as either licensed or unlicensed products, are listed in Table 1. The unlicensed products, and some licensed products that have not undergone Health Canada batch release, can be obtained under the Health Canada Special Access Program (SAP) (see legend in Table 1).

Table 1: Concentrates for hemostasis or hereditary angioedema, available or potentially available in Canada (see footnote for ordering information and dosage calculation)

<table>
<thead>
<tr>
<th>No.</th>
<th>Factor concentrate</th>
<th>Manufacturer</th>
<th>Specific viral inactivation/partitioning procedure†</th>
<th>Maximum specific activity (IU/mg protein)</th>
<th>Storage temp. (°C)/max RT(°C) x (months of storage)</th>
<th>Average in vivo recovery (IVR) (IU/dL per IU/kg infused)</th>
<th>Average T1/2 (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kovaltry™ †</td>
<td>Bayer Inc.</td>
<td>Solvent detergent/ nanofiltration</td>
<td>~ 4,000</td>
<td>2-8/25 (12)</td>
<td>2</td>
<td>13.8</td>
<td>Full length FVIII, no VWF</td>
</tr>
<tr>
<td>2</td>
<td>Xyntha™†</td>
<td>Pfizer</td>
<td>Solvent detergent/ nanofiltration</td>
<td>5,500–9,900</td>
<td>2-8/25 (3)</td>
<td>2.11</td>
<td>14.8</td>
<td>B-domain deleted FVIII, no VWF</td>
</tr>
<tr>
<td>3</td>
<td>Advate †</td>
<td>Shire</td>
<td>Solvent detergent</td>
<td>4,000–10,000</td>
<td>2-8/30 (6)</td>
<td>2.40</td>
<td>11.98</td>
<td>Full length FVIII, no VWF</td>
</tr>
<tr>
<td>4</td>
<td>Nuwiq®†</td>
<td>Octapharma</td>
<td>Solvent detergent/ nanofiltration</td>
<td>8,124</td>
<td>2-8/25 (1)</td>
<td>2.14</td>
<td>17.1 (age ≥12y) 12.5 (age &lt;12y)</td>
<td>B-domain deleted, no VWF</td>
</tr>
<tr>
<td>5</td>
<td>Zonovate® † (distributed by Héma-Québec only)</td>
<td>Novo Nordisk</td>
<td>Solvent detergent/nanofiltration</td>
<td>8,300</td>
<td>2-8/30 (12)</td>
<td>1.9 (age ≥12y) 2.0 (age 6–11y) 1.8 (age &lt;6y)</td>
<td>10.69 (age ≥12y) 8.92 (age 6–11y) 7.65 (age &lt;6y)</td>
<td>B-domain deleted, no VWF</td>
</tr>
<tr>
<td>6</td>
<td>Hemofil M †</td>
<td>Shire</td>
<td>Solvent detergent/ nanofiltration</td>
<td>2-22 (2,000 if albumin excluded)</td>
<td>2-30</td>
<td>2.0</td>
<td>14.8</td>
<td>High purity pdFVIII, full length FVIII, no VWF, formulated with albumin</td>
</tr>
<tr>
<td>7</td>
<td>Koate®-DVI †</td>
<td>Grifols</td>
<td>Solvent detergent/ terminal dry heat</td>
<td>9-22</td>
<td>2-8/25 (6)</td>
<td>2.0</td>
<td>16.12</td>
<td>pd full length FVIII, contains VWF (VWF:FVIII ratio 1.17:1), formulated with albumin</td>
</tr>
</tbody>
</table>

Published: Friday, August 24, 2018

Important disclaimer: This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
### Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

**N° Factor concentrate** | **Manufacturer** | **Specific viral inactivation/partitioning procedure§** | **Maximum specific activity (IU/mg protein)** | **Storage temp. (°C)/max RT(°C) x (months of storage) #** | **Average in vivo recovery (IVR) (IU/dL per IU/kg infused)** | **Average T₁/₂ (h)** | **Comments**
---|---|---|---|---|---|---|---
8 | Eloctate® † | Biogen-Idec | Solvent detergent/nanofiltration | 4,000-10,000 | 2-8/30 (6) | 2.24 | 19 | Recombinant fusion protein (B-domain deleted FVIII and dimeric Fc component of human IgG1), no VWF
9 | Adynovate® † | Shire | Solvent detergent | Data not available | 2-8/30 (3) | 2.66 (age ≥ 18y) 2.12 (age 12-17y) | 14.69 (age ≥ 18y) 13.43 (age 12-17y) | Recombinant FVIII conjugate with 20 kDa polyethylene glycol (PEGylated rFVIII)

**Factor VIII/VWF plasma-derived concentrate (pd FVIII/VWF) (licensed for von Willebrand disease and hemophilia A)**

10 | Humate P® † | CSL Behring | Pasteurization | FVIII: 1.3-2.6 VWF:RCo: 3.3-6.6 | 2-25 | FVIII: 2.0 VWF:RCo: 2.4 | FVIII: 12.2 VWF:RCo: 11 | VWF: FVIII ratio 2.4:1

11 | Wilate® † | Octapharma | Solvent detergent/terminal dry heat | ≥ 60 IU VWF:RCo ≥ 60 IU FVIII | 2-8/25 (6) | FVIII: 2.04 | FVIII: 15 | VWF: FVIII ratio 1:1

**Von Willebrand factor concentrate, recombinant (rVWF)**

12 | Vonvendi® | Shire | Data not available | Data not available | 2-30 | 1.5 | 19.1-22.6 | rVWF, no FVIII

**Porcine recombinant FVIII**

13 | Obizur® † | Shire | Solvent detergent/nanofiltration | 11,000-18,000 | 2-8 | PK not yet performed (for acquired hemophilia A) | PK not yet performed (for acquired hemophilia A) | rPorcine FVIII

**Factor IX recombinant (rFIX) – standard half-life**

14 | BeneFIX® † | Pfizer | Nanofiltration | ≥ 200 | 2-8/25 (6) | 0.8 (age > 15y); 0.7 (age less than or equal to 15y) | 18.8

15 | Rixubis® † (distributed by Héma-Québec only) | Shire | Solvent detergent/nanofiltration | ≥ 200 | 2-30 | 0.67 | 26.7

**Factor IX high purity plasma derived (pd) – standard half-life**

16 | Immunine® VH (hep) † | Shire | Vapour heating | 100 ± 50 | 2-8/25 (3) | 1.11 (age > 15y); 0.91 (age less than or equal to 15y) | 17 | Contains trace amount of heparin

**Factor IX recombinant – extended half-life**

17 | Aprolix® † | Boveratív | Nanofiltration | 45-63 | 2-8/30 (6) | 0.92 | 82.1 | Recombinant fusion protein of FIX and dimeric Fc component of human IgG1 (rFIXFc)

18 | Rebinyn® † | Novo Nordisk | Nanofiltration | 152 | 2-8/30 (6) | 1.9 (age ≥ 18y) 1.8 (age 13-17y) 1.15 (age ≥ 18y) 1.03 (age 13-17y) | Recombinant FIX conjugate with 40 kDa polyethylene glycol (PEGylated rFIX)

**Prothrombin Complex Concentrate (pd) (pd PCC)**

---

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.


Published: Friday, August 24, 2018
## Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

### Activated Prothrombin Complex Concentrate (pd) (pd aPCC)

<table>
<thead>
<tr>
<th>No</th>
<th>Factor concentrate</th>
<th>Manufacturer</th>
<th>Specific viral inactivation/partitioning procedure§</th>
<th>Maximum specific activity (IU/mg protein)</th>
<th>Storage temp. (°C)/max RT (°C) x (months of storage)</th>
<th>Average in vivo recovery (IVR) (IU/dL per IU/kg infused)</th>
<th>Average T_{1/2} (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>FEIBA NF†</td>
<td>Shire</td>
<td>Vapour heat/ nanofiltration</td>
<td>0.75–2.5</td>
<td>2–25</td>
<td>0.017 (g/L per mg/kg body weight infused)</td>
<td>77.1</td>
<td>No heparin added; FII, FVII, FIX and FX in relatively balanced ratio; 89-98% FVII activity attributed to FVIIa activity</td>
</tr>
<tr>
<td>22</td>
<td>RiaSTAP†</td>
<td>CSL Behring</td>
<td>Pasteurization</td>
<td>0.68 mg/mg†</td>
<td>2–25</td>
<td>400–700 mg of human albumin per 1 g concentrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Factor VII Concentrate†</td>
<td>Shire</td>
<td>Vapour heat/ nanofiltration</td>
<td>≇ 2</td>
<td>2–8</td>
<td>1.2–2.0</td>
<td>3–5</td>
<td>Heparin added</td>
</tr>
<tr>
<td>24</td>
<td>Niastase RT†</td>
<td>Novo Nordisk</td>
<td>Detergent/ nanofiltration</td>
<td>50,000</td>
<td>2–25</td>
<td>45.6% / 43.5% (non-bleeding / bleeding state)</td>
<td>2.9 / 2.3 (non-bleeding / bleeding state)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>HemoLeven†</td>
<td>LFB (France)</td>
<td>Solvent-detergent/ nanofiltration</td>
<td>Data not available</td>
<td>2–25</td>
<td>2–2.4</td>
<td>48</td>
<td>Heparin, AT and C-1 inhibitor added</td>
</tr>
<tr>
<td>26</td>
<td>Tretten†</td>
<td>Novo Nordisk</td>
<td>Not applicable</td>
<td>116–223</td>
<td>2–8</td>
<td>1.7</td>
<td>(11.5d)</td>
<td>Contains FXIII-A subunit only, not recommended for FXIII-B subunit deficiency</td>
</tr>
<tr>
<td>27</td>
<td>Corifact†</td>
<td>CSL Behring</td>
<td>Pasteurization/ nanofiltration</td>
<td>5.7–8.9</td>
<td>2–8</td>
<td>1.66</td>
<td>(6.6d)</td>
<td>Contains both FXIII-A and FXIII-B subunits</td>
</tr>
<tr>
<td>28</td>
<td>Antithrombin III NF†</td>
<td>Shire</td>
<td>Vapor heat, nanofiltration</td>
<td>1–2.5</td>
<td>2–8</td>
<td>2</td>
<td>(2.5d)</td>
<td>Heparin added</td>
</tr>
<tr>
<td>29</td>
<td>Ceprotin†</td>
<td>Shire</td>
<td>Pasteurization/detergent</td>
<td>Data not available</td>
<td>2–8</td>
<td>1.42</td>
<td>9.9</td>
<td>Human albumin added</td>
</tr>
<tr>
<td>30</td>
<td>Berinert®†</td>
<td>CSL Behring</td>
<td>Pasteurization, nanofiltration</td>
<td>Data not available</td>
<td>2–25</td>
<td>Data not available</td>
<td>87.7–91.4</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Cinryze®†</td>
<td>Shire</td>
<td>Pasteurization, nanofiltration</td>
<td>4.0–9.0 IU/mg protein</td>
<td>2–25</td>
<td>Data not available</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IVR = in vivo recovery; pd = plasma-derived; r = recombinant; RCo = Ristocetin cofactor; RT =
Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

room temperature; VWF = von Willebrand factor; 
T ½ = half-life; h = hour(s); d = day(s)

§Specific viral inactivation/partitioning procedure completed in addition to chromatographic fractionation/purification steps routinely used in the manufacturing process that are capable of removing virus particles.

¥ Maximum room temperature (RT) (usually ≤25°C or ≤30°C) storage period in months is stated only if the concentrate is to be stored refrigerated (2–8°C). Manufacturers recommend that once the concentrate has been removed from the required refrigeration and stored at RT, the date removed from refrigeration should be marked on the box and the product should not be returned to refrigeration.

† Health Canada licensed.


**Dosage calculation:** Use of average IVR for calculation of dosage to reach target factor level from baseline or measured factor level.

- Dosage in IU/kg = (target level in IU/dL factor activity - baseline or measured level in IU/dL factor activity) ÷ in vivo recovery (IVR) in IU/dL activity rise per IU/kg body weight infused)
- For fibrinogen concentrate (item 22): dosage in mg/kg body weight = (target fibrinogen level in g/L - baseline or measured fibrinogen level in g/L) ÷ IVR (in g/L per mg/kg body weight infused)

**Maintenance dose:**

The maintenance dose to reach the original peak factor concentration is half the original loading dose if the dosing interval is identical to the T½ for the clotting factor for the particular patient. Maintenance dose will vary if given at intervals different from T½ of the clotting factor for the particular patient (see Table 1 for average T½ of various clotting factors).

**Ordering:**

For licensed products: Canadian Blood Services or Héma-Québec;

For all unlicensed and some licensed products not yet batch-released by Health Canada: Health Canada SAP (www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php; Tel–office hours: 613-941-2108; off hours 613-941-3061)

**Notes:**

Recovery or IVR (activity in IU/dL recovered in circulation after 1 IU/kg infused) and half-life (T½) were established in patients with severe congenital deficiency (not in patients with acquired deficiency). For AT and protein C products, recovery and T½ are expected to be lower during acute thrombotic events.

Recovery and T½ indicated here are provided as rough guides only—the precise recovery and T½ may be different from patient to patient and can be determined by pharmacokinetic studies to help with more precise dosing and dosing intervals (see Chapter 17 of this Guide). Recovery tends to be lower in children, who have higher plasma volumes.

Table 1 is based on information available at time of update. This information is time-sensitive and will change regularly. Please refer to Canadian Blood Services’ Plasma Protein Products page for up-to-date information.


Published: Friday, August 24, 2018

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

Pharmacokinetic data (IVR, $T_{1/2}$) may be rounded or generalised; consult product monograph for product specific information.

**PLASMA-DERIVED VERSUS RECOMBINANT CONCENTRATES**

**Plasma-derived (pd)**

The majority of clotting factor concentrates are manufactured from pooled screened donor plasma.

**Recombinant (r)**

Recombinant clotting factor concentrates are manufactured using biotechnology. Recombinant clotting factors are expressed in cultured cell lines transfected with vectors carrying the clotting factor gene. The clotting factor protein secreted into the culture medium is purified and formulated for therapeutic use. Tables 2 and 3 provide information about the cell lines and the human/animal proteins used during the recombinant products manufacturing process or in the formulation, and the associated allergy precaution required for each recombinant product.

| Table 2: Cell lines used for the manufacturing of various recombinant factor concentrate |
|------------|------------------|------------------|
| **Cell lines** | **Recombinant concentrates** | **Allergy precaution** |
| Baby hamster kidney (BHK) | rFVIII: - Kovaltry™ (Bayer) rFVIII porcine: - Obizur® (Shire) rFVIIa: - Niastase RT® (Novo Nordisk) | Trace hamster proteins |
| Chinese hamster ovary (CHO) | rFVIII: - Advate (Shire) - Adynovate® (Shire) - Xyntha® (Pfizer) - Zonovate® (Novo Nordisk) rFIX: - BeneFIX® (Pfizer) - Rebinyn® (Novo Nordisk) - Rixubis® (Shire) rVWF: - Vonvendi® (Shire) | Trace hamster proteins |
| Human embryonic kidney (HEK) | rFVIII: - Nuwiq® (Octapharma) rFVIIIIFc: - Eloctate® (Biogen Idec) rFIXFc: - Alprolix® (Biogen Idec) | |
| Yeast (Saccharomyces cerevisiae) | rFXIII: - Tretten® (Novo Nordisk) | Trace yeast proteins |

| Table 3: Human/animal proteins that may be present during the manufacturing process (cell culturing or purification) or in formulation in recombinant factor concentrates |
|------------------|------------------|------------------|
| **Proteins** | **Recombinant concentrates** | **Allergy precaution** |
| Solid phase mouse monoclonal antibody - for purification step | rFVIII: - Advate® (Shire) - Adynovate® (Shire) - Kovaltry™ (Bayer) - Zonovate® (Novo Nordisk) | Trace mouse proteins |

Published: Friday, August 24, 2018

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
Proteins | Recombinant concentrates | Allergy precaution
--- | --- | ---
Concentrate of porcine protein | Porcine rFVIII – Obizur® (Shire) | Porcine protein
Human serum albumin in formulation | Human serum albumin no longer used in recombinant products currently available in Canada | 

**VIRAL SAFETY**

The chromatographic process used during fractionation and purification of the clotting factors reduces the viral load.

Additionally, virus inactivation/partitioning procedures are incorporated into the manufacturing process for all pd concentrates and most of the recombinant concentrates (see Table 1).

- The virus inactivation procedures are all effective against important human pathogens such as human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV). In Canada, virus-inactivated factor concentrates were introduced in 1985. No case of HIV or HCV transmission due to concentrate use has occurred since 1987 and 1988, respectively.
- However, no virus inactivation procedure is expected to inactivate all viruses. In particular, non-enveloped viruses such as parvovirus B19, a pathogen in immunosuppressed patients, can be resistant to viral inactivation processes.

Patients with congenital coagulation deficiency who are expected to receive any blood product(s) should be immunized against HBV and hepatitis A virus (HAV).

Transmission of Creutzfeld-Jakob disease (CJD) and variant CJD is considered a theoretical risk for pd concentrates.

**PREVENTION OF THROMBOTIC COMPLICATIONS**

Clotting factor concentrates affect hemostasis by correcting the underlying clotting defect.

- Patients with coagulation factor deficiency and with coexisting risk factors for thrombosis or disseminated intravascular coagulation (DIC) may develop thrombotic complications when the hemostatic mechanism is corrected.
- Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC), factor eight inhibitor bypass activity (FEIBA), factor XI (FXI) concentrate and recombinant factor VIIIa (rFVIIIa) should be used with caution in patients with risk factors for thrombosis or DIC, such as sepsis, crush injury, atherosclerosis and advanced age.
- Prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC): not indicated for liver disease, DIC or patients with active arterial or venous thromboembolism.
- The dosage for FEIBA should not exceed 200 IU/kg/day.
- The dosage for FXI concentrate should not exceed 30 IU/kg per dose.
- Thrombosis has been reported in patients with von Willebrand disease (VWD), treated to raise factor VIII (FVIII) level in excess of 200 IU/dL (2 IU/ml) in the surgical setting.
- Antifibrinolytic therapy should be avoided when using PCC and aPCC (including FEIBA).

Several plasma-derived concentrates contain heparin (Factor VII concentrate [Shire], FXI Hemoleven® [FLB], FIX Immune® VH [Shire], PCC Beriplex® P/N [CSL Behring], PCC Octaplex® [Octapharma], Antithrombin III NF
CLINICAL GUIDE TO TRANSFUSION

Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

[Shire]; see Table 1). These concentrates should be avoided in patients with a history of heparin-induced thrombocytopenia.

ALLERGY PRECAUTIONS

As with infusion of any protein products, allergic reactions may occur.

- Minor allergic reactions may be prevented by pre-medication with antihistamines.
- When an allergic reaction occurs, a similar concentrate from a different manufacturer can be used for subsequent treatment and may not result in an allergic response.
- Patients on home-therapy should have epinephrine (e.g. Epipen®) on hand to deal with serious allergic reactions or anaphylaxis.
- Some recombinant concentrates may contain trace amount of non-human proteins as indicated in Tables 2 and 3. The manufacturers suggest caution in the use of their respective products in patients with known allergy to these proteins. Recombinant porcine FVIII is of porcine protein in nature.

Hemophilia B patients may have severe allergic responses (including anaphylaxis) to concentrates containing factor IX (FIX) (including prothrombin complex concentrates and FEIBA) at the time inhibitors are developing.

- In susceptible severe hemophilia B patients, inhibitors develop usually early on with FIX concentrate treatment.
- It is advisable to treat newly diagnosed severe hemophilia B patients in a setting equipped for management of severe allergic reactions during at least approximately the first 20 treatments.

STORAGE AND TRANSPORTATION

Coagulation factor concentrates are stable until the printed expiration date on the vials (or boxes) when stored at the specified temperature.

- For products that are to be refrigerated at 2–8°C (see Table 1), long distance transportation must occur in validated transport containers cooled with cold packs.
- Some, but not all, of these concentrates can be stored at RT (usually ≤25°C or ≤ 30°C) for a specified period after removing from the refrigerated temperature (see Table 1).
- When it is necessary to store these products at RT, the date when the box is removed from refrigeration must be clearly marked on the box, and the manufacturers do not recommend returning these RT stored concentrates to refrigeration.
- Storage of concentrates at freezing temperature should be avoided.

RECONSTITUTION

Almost all clotting factor concentrates available to Canadian patients are supplied in packages containing a kit for reconstitution and infusion, usually with the appropriate diluent.

Many manufacturers also provide proprietary devices for transferring diluent into the vial containing the lyophilized concentrate and for withdrawing the dissolved concentrate to syringes for infusion. The reconstitution instructions in the product insert must be followed and aseptic techniques observed.

In general, the vials of diluent and concentrate should be at RT (or pre-warmed to 20–37°C for refrigerated products) before mixing. The diluent should, if possible, be allowed to flow down the side of the vial wall and the...
mixture should then be swirled gently to allow dissolution of the concentrate. Shaking must be avoided as it may create bubbles/foam and result in denaturation of the proteins.

SPECIFIC PROPERTIES AND INDICATIONS OF FACTOR CONCENTRATES

Table 1 provides the properties and other characteristics of individual factor concentrates.

Table 4 below provides indications, monitoring, contraindications/precautions and available alternatives for different classes of factor concentrates. For specific product information refer to the package insert provided by the manufacturer of each concentrate.

Table 4: Use of coagulation factor concentrates (see footnote for calculation of dosage)

<table>
<thead>
<tr>
<th>Item No. (refer to Table 1)</th>
<th>Factor concentrate</th>
<th>Indications (for treatment and prophylaxis)*</th>
<th>Monitoring</th>
<th>Contraindications/precautions</th>
<th>Available alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>rFVIII (standard half-life)</td>
<td>• Hemophilia A</td>
<td>• FVIII level</td>
<td>• Not for VWD – concentrates contain no VWF</td>
<td>• pd FVIII (standard half-life) • rFVIII (extended half-life) • Desmopressin for responsive mild patients • Cryoprecipitate • pdFVIII/VWF concentrate</td>
</tr>
<tr>
<td>6-7</td>
<td>High purity pdFVIII (standard half-life)</td>
<td>• Hemophilia A</td>
<td>• FVIII level</td>
<td>• Not for VWD – concentrates contain no VWF</td>
<td>• rFVIII (standard half-life) • rFVIII (extended half-life) • Desmopressin for responsive mild patients • Cryoprecipitate • pdFVIII/VWF concentrate</td>
</tr>
</tbody>
</table>

Published: Friday, August 24, 2018

Important disclaimer: This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
## Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Factor concentrate</th>
<th>Indications (for treatment and prophylaxis)*</th>
<th>Monitoring</th>
<th>Contraindications/precautions</th>
<th>Available alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-9</td>
<td>rFVIIIf (extended half-life)</td>
<td>• Hemophilia A • FVIII level</td>
<td>• Not for VWD – concentrates contain no VWF</td>
<td>• rFVIII (standard half-life) • pdFVIII (standard half-life) • Desmopressin for responsive mild patients • Cryoprecipitate • pdFVIII/VWF concentrate</td>
<td></td>
</tr>
<tr>
<td>10-11</td>
<td>pd FVIII/VWF</td>
<td>• VWD • Hemophilia A • VWF:RCo / activity level, VWF:Ag level, FVIII levels • FVIII level</td>
<td>• FVIII: VWF ratio varies (see Table 1) • Keep FVIII &lt; 200 IU/dL (thrombosis precaution) especially in surgical setting</td>
<td>• rVWF (for VWD only) • Desmopressin for ○ responsive types 1 and 2A VWD patients ○ responsive Hemophilia A • Cryoprecipitate</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>rVWF</td>
<td>• VWD • Acquired hemophilia A (with autoimmune FVIII inhibitor antibodies) • VWF:RCo / activity level, VWF:Ag level, FVIII levels</td>
<td>• Not for hemophilia A – concentrate contains no FVIII</td>
<td>• pd FVIII/VWF • Desmopressin for ○ responsive types 1 and 2A VWD patients • Cryoprecipitate</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>rPorcine FVIII</td>
<td>• Acquired hemophilia A (with autoimmune FVIII inhibitor antibodies) • FVIII level</td>
<td>• Currently licensed only for patients with acquired autoantibodies/inhibitors against FVIII</td>
<td>• FEIBA • rFVIIa</td>
<td></td>
</tr>
<tr>
<td>14-15</td>
<td>rFIX (standard half-life)</td>
<td>• Acquired hemophilia A (with autoimmune FVIII inhibitor antibodies) • Acquired hemophilia A (with autoimmune FVIII inhibitor antibodies) • FVIII level</td>
<td>• −50% of FIX inhibitor patients may develop a severe allergic reaction at time of inhibitor development • These patients may develop nephrotic syndrome with ITI</td>
<td>• pd FIX (Standard half-life) • rFIX (extended half-life)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>High purity pd FIX (standard half-life)</td>
<td>• Hemophilia B • FIX level</td>
<td>• See rFIX above • Patients with heparin-induced thrombocytopenia</td>
<td>• rFIX (standard half-life) • rFIX (extended half-life)</td>
<td></td>
</tr>
</tbody>
</table>

---


Published: Friday, August 24, 2018

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for **adult patients** and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
## Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

### Table 1: Indications for Treatment and Prophylaxis

<table>
<thead>
<tr>
<th>Item N° (refer to Table 1)</th>
<th>Factor concentrate</th>
<th>Indications (for treatment and prophylaxis)*</th>
<th>Monitoring</th>
<th>Contraindications/precautions</th>
<th>Available alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-18 rFIX (extended half-life)</td>
<td>• Hemophilia B</td>
<td>• FIX level</td>
<td>• See rFIX above</td>
<td></td>
<td>• rFIX (standard half-life) • pd FIX (standard half-life)</td>
</tr>
<tr>
<td>19-20 pd PCC, non-activated (contains FII, FVII, FIX, FX)</td>
<td>• Rapid reversal of warfarin overdose, vitamin K deficiency • FX deficiency • FII deficiency</td>
<td>• INR</td>
<td>• Thrombotic precaution • Liver disease, DIC, active or having risk factors for arterial/venous thrombosis • IgA deficient donors with anti-IgA (Octaplex®) • Patients with heparin-induced thrombocytopenia</td>
<td>• Plasma§ • Plasma§ • Plasma§</td>
<td></td>
</tr>
<tr>
<td>21 pd aPCC</td>
<td>• FVIII inhibitor (congenital or acquired) • FIX inhibitor</td>
<td>• Clinical</td>
<td>• FVIII inhibitor: may cause anamnesis – avoid while patient is waiting for ITI but can be used for bleed treatment &amp; prophylaxis during ITI • FIX inhibitor: do not use if patient has allergic reactions to FIX • Thrombotic precaution – limit dosage to 200 IU/kg/d</td>
<td>• FVIII inhibitor: rFVIIa, rPorcine FVIII • FIX inhibitor: rFVIIa</td>
<td></td>
</tr>
<tr>
<td>22 pd Fibrinogen</td>
<td>• Congenital fibrinogen deficiency</td>
<td>• Fibrinogen level</td>
<td>• Manifest thrombosis &amp; myocardial infarction, except in cases of potentially fatal bleeding</td>
<td>• Cryoprecipitate (~200 mg/bag)</td>
<td></td>
</tr>
<tr>
<td>23 pd FVII</td>
<td>• FVII deficiency</td>
<td>• FVII level</td>
<td>• Patients with heparin-induced thrombocytopenia</td>
<td>• rFVIIa</td>
<td></td>
</tr>
</tbody>
</table>

---

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for **adult patients** and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
## Concentrates for Hemostatic Disorders and Hereditary Angioedema

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Factor concentrate</th>
<th>Indications (for treatment and prophylaxis)*</th>
<th>Monitoring</th>
<th>Contraindications/precautions</th>
<th>Available alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>rFVIIa</td>
<td>• FVIII inhibitor • FIX inhibitor • FVII deficiency (each microgram contains 50 IU FVIIa) • Glanzmann’s thrombasthenia (with platelet antibodies and/or refractoriness or when platelets not available)</td>
<td>Clinical • Clinical • FVII level • Clinical</td>
<td>Thrombosis precaution</td>
<td>• FVIII inhibitor: FEIBA, rPorcine FVIII • FIX inhibitor: FEIBA • FVII deficiency: pd FVII, pd PCC, Plasma§</td>
</tr>
<tr>
<td>25</td>
<td>pd FXI</td>
<td>• FXI deficiency</td>
<td>FXI level</td>
<td>Thrombosis precaution – limit dosage to ≤ 30 IU/kg • Patients with heparin-induced thrombocytopenia</td>
<td>Plasma§</td>
</tr>
<tr>
<td>26</td>
<td>rFXIII</td>
<td>• FXIII A-subunit deficiency</td>
<td>FXIII level</td>
<td>Not recommended for FXIII B-subunit deficiency • In cases of fresh thrombosis, exercise caution due to the fibrin-stabilizing effect</td>
<td>pd FXIII • Plasma§ • Cryoprecipitate (50–75 IU FXIII per bag)</td>
</tr>
<tr>
<td>27</td>
<td>pd FXIII</td>
<td>• FXIII (A- or B-subunit) deficiency</td>
<td>FXIII level</td>
<td>In cases of fresh thrombosis, exercise caution due to the fibrin-stabilizing effect</td>
<td>rFXIII if FXIII A-subunit deficiency (not for FXIII B-subunit deficiency) • Plasma§ • Cryoprecipitate (50–75 IU FXIII per bag)</td>
</tr>
</tbody>
</table>


Published: Friday, August 24, 2018

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.
## Chapter 5: Concentrates for Hemostatic Disorders and Hereditary Angioedema

<table>
<thead>
<tr>
<th>Item No (refer to Table 1)</th>
<th>Factor concentrate</th>
<th>Indications (for treatment and prophylaxis)*</th>
<th>Monitoring</th>
<th>Contraindications/precautions</th>
<th>Available alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>pd antithrombin</td>
<td>• AT deficiency in high thrombotic risk situation such as surgery</td>
<td>• AT level</td>
<td>• Patients with known history of heparin-induced thrombocytopenia</td>
<td>• Plasma§</td>
</tr>
<tr>
<td>29</td>
<td>pd protein C</td>
<td>• Severe protein C deficiency (homozygous/ double heterozygous)</td>
<td>• Protein C level</td>
<td></td>
<td>• Plasma§</td>
</tr>
<tr>
<td>30-31</td>
<td>pd C1-INH</td>
<td>• Hereditary Angioedema</td>
<td>• N/A</td>
<td></td>
<td>• Plasma</td>
</tr>
</tbody>
</table>

Abbreviations: aPCC = activated Prothrombin Complex Concentrate; AT = antithrombin; FEIBA = Factor eight inhibitor bypass activity; INR = International Normalized Ratio; ITI = Immune Tolerance Induction; PCC = prothrombin complex concentrate; pd = plasma derived; RCo = Ristocetin Cofactor; VWD = von Willebrand disease; VWF = von Willebrand Factor;

§ Plasma: fresh frozen plasma, frozen plasma or virus inactivated plasma such as Octaplasma® (Octapharma).

**Dosing for various indications:** (Please refer to Chapter 17 of this Guide for desired dosage for various hemostatic challenges).

### Coagulation Factors Items 1-27:

**Dosage calculation:**

- Items 1-21, 23-27: Dosage in IU/kg = (target level in IU/dL factor activity - baseline or measured level in IU/dL factor activity) / IVR (where IVR = in vivo recovery in IU/dL activity rise per IU/kg body weight infused) [see Table 1 for IVR of various clotting factors].
- Item 22 (fibrinogen concentrate): dosage in mg/kg (body weight) = (target fibrinogen level in g/L - baseline or measured fibrinogen level in g/L) / IVR (in g/L per mg/kg body weight infused)

**Maintenance dose:**

The maintenance dose to reach the original peak factor concentration is half the original loading dose if the dosing interval is identical to the T₁/₂ for the clotting factor for the particular patient. Maintenance dose will vary if given at intervals different from T₁/₂ of the clotting factor for the particular patient. [see Table 1 for average T₁/₂ of various clotting factors].

### Coagulation Factors Items 28-29:

Antithrombin concentrate (item 28) for congenital antithrombin deficiency:

Antithrombin concentrate together with heparin has been used in patients with inherited antithrombin deficiency and heparin resistance, as prophylaxis for surgery, trauma, immobilization, and thromboembolism during pregnancy as well as after delivery, with favourable results. There are, however, no randomized clinical trials to establish efficacy. One recommendation for dosage calculation is as follows: Loading dose: \((\text{target minus current AT level in IU/dL} \times \text{weight (kg)}) ÷ 1.4\); maintenance dose: \(-60\%\) loading dose every 24h to maintain peak AT level at \(-120\) IU/dL and trough level at \(-80\) IU/dL.

**Protein C concentrate (item 29) for congenital protein C deficiency:**


Patients with homozygous or compound heterozygous protein C deficiency typically present with skin necrosis within the first two weeks of postnatal life. Replacement therapy with protein C concentrate at a dose of 100 IU/kg followed by 50 IU/kg every 6 hours to maintain a trough protein C level of about 50 IU/dL (as well as decreasing or normalization of D-dimer level) can be used.

For long-term prophylaxis in patients with severe protein C deficiency (homozygous/compound heterozygous), maintenance subcutaneous (or intravenous) doses of 30–50 IU/kg every one to two days or warfarin (initiated after full heparinization for several days to prevent skin necrosis) to maintain INR 2.5–3.5 (or INR 1.5–2.5 together with protein C replacement) have been used. Monitoring with D-dimer level for evidence of coagulation activation is useful to confirm adequate replacement or anticoagulation therapy.

**FURTHER READING AND SOURCES**

The product monographs/package inserts should be consulted for further information about the various products discussed in this chapter. See Chapter 17 of this *Guide* for more information on hemostatic disorders.

The information presented in this chapter was obtained from the individual manufacturers, usually vetted through their medical/scientific and regulatory departments, and from product monographs available online. Where possible, data from different sources were compared to each other and to the literature. It should be noted that parameters such as average IVR and T1/2 are approximate and may differ slightly from different sources including those from different studies and different phases of clinical trials.

**CONTINUING PROFESSIONAL DEVELOPMENT CREDITS**

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) program can claim the reading of the *Clinical Guide to Transfusion* as a continuing professional development (CPD) activity under Section 2: Self-learning credit. The reading of one chapter is equivalent to two credits.

**ACKNOWLEDGEMENTS**

The authors acknowledge William Sheffield, PhD, for his review of this chapter.

We're here to answer your questions about the *Clinical Guide to Transfusion*. We'd also appreciate your ideas on how to improve the Guide. Please contact us through the *Clinical Guide feedback form*. 

Published: Friday, August 24, 2018

**Important disclaimer:** This material is an educational tool providing guidelines for the care of patients. These recommendations should thus not be applied rigidly, since they could result in some patients receiving unnecessary transfusions or experiencing adverse effects from under-transfusion. The guidelines are mainly for adult patients and may not necessarily apply to the treatment of children. The recommendations do not replace the need in some cases to consult an expert in Transfusion Medicine to provide optimal patient care.