UP Health System - Marquette  
Pharmacy and Therapeutics Committee  
Medication Guideline  

**Drug Classification:** 20:28.16 Hemostatics

| Agent:                                                                 | Formulary
top | Nonformulary | Restricted | Nonstock |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inhibitor coagulant complex (Feiba NF®)</td>
<td>X</td>
</tr>
<tr>
<td>Anti-Hemophilic Factor, Human (Factor VIII; AHF) (Monoclate-P®, Koate®, Hemofil®, Monarc®)</td>
<td>X</td>
</tr>
<tr>
<td>Antihemophilic Factor, Recombinant (Recombinate®, Advate®, Helixate®, Kogenate®, ReFacto®, Xyntha®)</td>
<td>X</td>
</tr>
<tr>
<td>Antithrombin III (ATryn®, Thrombate III®)</td>
<td>X</td>
</tr>
<tr>
<td>Coagulation Factor VIIa, Recombinant (Novaseven RT®)</td>
<td>X</td>
</tr>
<tr>
<td>Factor IX, recombinant (Alphanine®, Benefix®, Mononine®)</td>
<td>X</td>
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<tr>
<td>Factor IX Complex (Beblulin VH®, Profilnine®, Kcentra®)</td>
<td>X</td>
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<tr>
<td>Factor XIII concentrate (Human) (Corifact®)</td>
<td>X</td>
</tr>
<tr>
<td>Antihemophilic Factor/von Willebrand Factor Complex (Factor VIII/VWF; AHF/VWF) (Humate-P®, Alphanate)</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup>Formularybrand is in bold

**Pharmacy and Therapeutics Committee-approved Indications for Inpatient Use:**
- Formulary blood factors are approved for use according to the indications listed below. Recommended doses may vary from labeling depending upon patient need and clinical situation.

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Control of bleeding episodes in hemophilia A&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Anti-hemophilic Factor, Recombinant (Recombinate®) | Mild hemorrhage (hemarthrosis, muscle bleeding, mild oral bleeding)  
  - **Dose sufficient to achieve a level of 20% to 40% of normal. Begin every 12 to 24 hours for 1 to 3 days until the bleeding episode is resolved.**  
  - Moderate hemorrhage (more extensive hemarthrosis, muscle bleeding or hematoma  
    - **Dose sufficient to achieve a level of 30% to 60% of normal. Repeat every 12 to 24 hours for 3 days or more.**  
  - Major hemorrhage (life-threatening, head injury, throat bleeding, severe abdominal pain  
    - **Dose sufficient to achieve a level of 60% to 100% of normal. Repeat every 8 to 24 hours until resolution of bleeding episode** |

<table>
<thead>
<tr>
<th>Antithrombin III (Thrombate III®)</th>
<th>Perioperative management of patients with hemophilia A&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Minor:</em></td>
<td>A single infusion to achieve a peak post infusion factor VIII activity of 60% to 80% of normal in combination with oral antifibrinolytic therapy.</td>
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<tr>
<td><em>Major:</em></td>
<td>A single infusion to achieve a peak post infusion factor VIII activity of 80% to 100% pre- and postoperatively. Repeat infusion every 8 to 24 hours, depending on state of healing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation Factor VIIa, Recombinant (Novaseven RT®)</th>
<th>Restricted to cardiothoracic surgery/anesthesia for use in antithrombin III-deficient patients undergoing cardiopulmonary bypass</th>
</tr>
</thead>
</table>
| *500 IU vial (actual potency will vary and is stated on the vial label) should result in an activated clotting time (ACT) of at least 400 seconds after standard heparin dosing*  
*If an adequate response is not observed, administration of an additional vials for a total of two vials (~1,000 IU) per patient should be considered* |

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<thead>
<tr>
<th>Coagulation Factor VIIa, Recombinant (Novaseven RT®)</th>
<th>Acquired hemophilia:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>70 to 90 mcg/kg by slow bolus injection repeated every 2 to 3 hours until hemostasis achieved. The minimum effective dose has not been determined</em></td>
<td></td>
</tr>
</tbody>
</table>
**Hemophilia A or B patients with inhibitors to factor VIII or factor IX:**
- Bleeding episodes:
  - Dose: 90mcg/kg every 2 hours until hemostasis is achieved, or until the treatment has been judged to be inadequate. The minimal effective dose has not been established.
- Surgical Interventions:
  - Dose: 90mcg/kg immediately before surgery and repeated every 2 hours for the duration of the surgery
  - Duration: For minor surgery, postsurgical dosing every 2 hours for the first 48 hours, then every 2 to 6 hours until healing has occurred. For major surgery, postsurgical dosing every 2 hours for 5 days, then every 4 hours until healing has occurred.

**Congenital Factor VII deficiency:**
- Bleeding episodes and surgical interventions:
  - 15 to 30mcg/kg every 4 to 6 hours until hemostasis achieved. The minimal effective dose has not been determined.

**Factor IX (Benefix®)**

**Prevention and control of bleeding in factor IX deficiency (hemophilia B [Christmas disease]).^**

**Perioperative management of hemophilia B^**
- Minor hemorrhage (uncomplicated hemarthrosis, superficial muscle, or soft tissue).
  - Dose to achieve 20% to 30% factor IX activity every 12 to 24 hours for 1 to 2 days
- Moderate hemorrhage (Intramuscular or soft tissue with dissection, mucous membranes, dental extractions, or hematuria)
  - Dose to achieve 25% to 50% factor IX activity every 12 to 24 hours. Treat until bleeding stops and healing begins; about 2 to 7 days.
- Major hemorrhage (Pharynx, retropharynx, retroperitoneum, CNS, surgery)
  - Dose to achieve 50% to 100% factor IX activity every 12 to 24 hours for 7 to 10 days.

**Factor IX Complex (Kcentra®)**

**Urgent reversal of warfarin (Coumadin®) therapy in adult patients with acute major bleeding unable to receive alternative therapy such as fresh frozen plasma. It is not indicated for reversal of warfarin therapy in adult patients without acute major bleeding.**
- Give with 5-10mg vitamin K
  - 25units/kg for INR 2 to <4 (do not exceed 2500units)
  - 35units/kg for INR 4 to 6 (do not exceed 3500units)
  - 50units/kg for INR>6 (do not exceed 5000units)
  - Dose should not be repeated
- Rivaroxaban (Xarelto®), Apixaban (Eliquis®)
  - 25 units/kg. May repeat x 1.

**Antihemophilic Factor/von Willebrand Factor Complex (Humate-P®)**

**Treatment and Prevention of bleeding in Hemophilia A^**
- Minor hemorrhage (Early joint or muscle bleed, severe epistaxis)
  - 15 units/kg to achieve factor VIII:C. plasma level 30% of normal. May repeat half the dose once or twice daily for 1 to 2 days
- Moderate hemorrhage (Advanced joint or muscle bleed, neck, tongue or pharyngeal hematoma without airway compromise, tooth extraction, severe abdominal pain)
  - 25 units/kg to achieve factor VIII:C. plasma level 50% of normal, followed by 15 units/kg every 8 to 12 hours for first 1 to 2 days, then same dose once or twice a day for a total of up to 7 days, or until adequate wound healing.
- Life-threatening hemorrhage (Major operations, GI bleeding, neck, tongue, or pharyngeal hematoma with potential airway compromise, intracranial, intra-abdominal or intrathoracic bleeding, fractures)
  - 40 to 50 units/kg, followed by 20 to 25 units/kg every 8 hours to maintain factor VIII:C. plasma level at 80 to 100% of normal for 7 days, then continue the same dose once or twice a day for another 7 days in order to maintain the VIII:C. level at 30% to 50% of normal

**Von Willebrand Disease^**
- Treatment of bleeding episodes and prevention of excessive bleeding during and after surgery.
  - 40-80 units of VWF:RCo (corresponding to 17 to 33 units of factor VIII in AHF/VWF) per kilogram body weight are given every 8 to 12 hours. Repeat doses are administered for as long as needed based on repeat monitoring of appropriate clinical and laboratory measures

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*Calculation: Dosage required (units) = [body weight (kg) x desired % factor VIII increase/2% per units/kg] Dosage must be individualized according to needs of the patient, severity of the deficiency, severity of hemorrhage, presence of inhibitors, and the factor VIII level desired. It is often critical to follow the factor VIII levels. The clinical effect of factor VIII is the most important element in evaluating the effectiveness of treatment.*

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*Calculation: number of factor IX units required = body weight (kg) × desired factor IX increase (% or units/dL) × reciprocal of observed recovery (units/kg vs per units/dL). In previously treated adults, on average, 1 unit of BeneFix per kg of body weight increased the circulating activity of factor IX by 0.8 ± 0.2 (range, 0.4 to 1.2) units/dL. Doses should be titrated using the factor IX activity and pharmacokinetic parameters.*

*Calculation: body weight (kg) × desired factor IX increase (% or normal) × 1.2 = number of factor IX units required. Exact dosage determination based on localization and extent of hemorrhage and the level of factor IX to be achieved. Close laboratory monitoring of the factor IX level is required to determine proper dosage.*

1 unit of factor VIII activity per kilogram body weight will increase the circulating factor VIII level by approximately 2 units/dL.

Expected levels of VWF:RCo are based on an expected in vivo recovery of 2 units/dL rise per unit/kg of VWF:RCo administered.

**Administration:**
- In general, all formulary coagulation factors are supplied by the manufacturer in a kit which contains drug, diluent and filter needle or spike. Most are given by slow IV bolus injection. See table below for specific administration.

<table>
<thead>
<tr>
<th>Blood Factor</th>
<th>Rate of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-hemophilic Factor, Recombinant (Recombinate®)</td>
<td>Can be administered within 5 minutes (max rate = 10ml/min). If pulse markedly increases, decrease rate or temporarily halt infusion.</td>
</tr>
<tr>
<td>Antithrombin III (Thrombate III®)</td>
<td>Can be infused over 10 to 20 minutes</td>
</tr>
<tr>
<td>Coagulation Factor VIIa, Recombinant (Novoseven RT®)</td>
<td>Slow bolus over 2 to 5 minutes</td>
</tr>
<tr>
<td>Factor IX (Benefix®)</td>
<td>Infuse slowly over several minutes. Rate of administration determined by the response and comfort of the patient.</td>
</tr>
<tr>
<td>Factor IX Complex (Kcentra®)</td>
<td>Infuse at a rate of 0.12ml/kg/min, up to max rate of 8.4ml/min Do not allow blood to enter the syringe as a fibrin clot may form.</td>
</tr>
<tr>
<td>Antihemophilic Factor/von Willebrand Factor Complex (Humate-P®)</td>
<td>Infuse at 2 to 4ml/min. If pulse markedly increases, decrease rate or temporarily halt infusion.</td>
</tr>
</tbody>
</table>

**Monitoring / Outcomes:**
Monitor for signs of bleeding, hemostasis, and hypersensitivity reactions.

**Laboratory Values:**
- Factor activity of the factor being replaced.
- Development of inhibitors.
- PT/INR and PTT have no correlation with achieving hemostasis but may be useful as an adjunct test to evaluate efficacy and guide dose adjustments (Novoseven®).
- Heart rate and blood pressure before and during IV administration.

**FDA Warnings:**
- **Increased risk for thromboembolic complications:**
  - Warning for all formulary coagulation factors except Anti-hemophilic Factor, Recombinant (Recombinate®)
  - Coagulation Factor VIIa, Recombinant (Novoseven RT®) has a black box warning:
    - Serious arterial and venous thrombotic and thromboembolic adverse events, including fatalities, are associated with the use outside labeling indications. Patients should be advised and monitored on the signs/symptoms of thrombotic and thromboembolic events.
  - Factor IX Complex (Kcentra®) black box warning:
    - Arterial and venous thromboembolic complication because patient being treated with warfarin have underlying disease states that predispose them to thromboembolic events. Benefits of reversing warfarin should be weighed against the potential risks of thromboembolic events, especially in...
patients with the history of a thromboembolic event. Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months (patients were excluded from studies).

- **Development of factor inhibitors (neutralizing antibodies)**
  - Diminished clinical response may be an indication of factor inhibitor development
  - Anti-hemophilic Factor, Recombinant (Recombinate®) - Incidence of development of Factor VIII inhibitor is 31.7% with use
  - Coagulation Factor VIIa, Recombinant (Novoseven RT®) can cause development of antibodies in factor VII deficient patients
  - Factor IX (Benefix®) - increased likelihood of hypersensitivity/anaphylactic reactions in patient who develop factor IX inhibitors with use

- **Transmission of disease - Factor IX Complex (Kcentra®), Antihemophilic Factor/von Willebrand Factor Complex (Humate-P®), Antithrombin III (Thrombate III®)**
  - Derived from human plasma – potential risk for transmission of infection, including theoretical risk for transmission of Creutzfeldt-Jakob disease
  - Use with caution in immune-compromised patients – product may contain parvovirus B19 and/or hepatitis A

**Special Handling Procedures:**
- Coagulation factors are not considered hazardous drugs.
- Coagulation factors are not considered high-alert drugs.