Factor Concentrates

Overview:

This section is intended to provide general information on products that may be indicated for use in patients with certain congenital or acquired bleeding disorders. Suggested treatment options are also included for patients on warfarin or direct oral anticoagulant (DOAC) when there is active bleeding or need for urgent/emergent invasive procedures.

Consult pharmacy services at your institution for information about drug availability, dosage and routes for administration. Any off-label use of products must be reviewed and determined by each institution. Consider consultation with hematologist or other specialist as appropriate for treatment options and dosing.

There are multiple factor concentrates available for use in treatment of patients with bleeding disorders. Selected factor concentrate products are listed below and may be available through Versiti Drug Distribution Services in Wisconsin and Illinois (see http://www.versiti.org/medical-professionals/products-services/pharmacy).

Summary of Bleeding Disorders and Common Factor Concentrates Used for Treatment

Congenital Disorders:

Hemophilia A (Factor VIII deficiency)

- Kogenate®FS (Bayer)
  - Recombinant product
  - Available in single use vials; nominal dose of either 250, 500, 1000, 2000, or 3000 IU
  - Approved for use in adults and children
- Hemofil M (Takeda)
  - Plasma derived product – monoclonal antibody purification
  - Available in single use vials; approximate dose of either 250, 500, 1000 or 1700 IU
  - Approved for use in adults
- Eloctate (Bioverativ Therapeutics) – Factor VIII, Fc fusion protein
  - Recombinant DNA-derived product
  - Available in single use vials; nominal dose of either 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, or 6000 IU
  - Approved for use in adults and children
- JIVI (Bayer) – Factor VIII, PEGylated-aucl
  - Recombinant DNA-derived product
  - Available in single use vials; nominal dose of either 500, 1000, 2000 or 3000 IU
  - Approved for use in adults and children 12 years of age and older
- DDAVP (Desmopressin) Injection (Sanofi)
  - Approved for use in adults and children over 2 years of age

- Each vial contains 4 mcg/mL of Desmopression acetate
- For treatment of mild hemophilia A (Factor VIII level 5-40%)

Hemophilia B (Factor IX deficiency)

- BeneFIX® (Pfizer)
  - Recombinant product
  - Available in single use vials; approximate dose of either 250, 500, 1000, 2000 or 3000 IU
  - Approved for use in adults and children
- Rixubis® (Shire)
  - Recombinant product
  - Available in single use vials; approximate dose of either 250, 500, 1000, 2000 or 3000 IU
  - Approved for use in adults and children
- Alprolix® (Bioverativ Therapeutics) – Factor IX, FC fusion protein
  - Recombinant DNA-derived product
  - Available in single use vials; nominal dose of either 250, 500, 1000, 2000, 3000, or 4000 IU
  - Approved for use in adults and children
- Kcentra (CSL Behring)
  - Plasma derived product that contains inactive forms of 4 coagulation factors (Factor II, VII, IX and X), and antithrombotic Proteins C and S. Known as **4F-PCC**.
  - Kcentra potency (units) is defined by Factor IX content. Dose is based on actual potency which is stated on the vial and will vary from 20-31 Factor IX units/mL after reconstitution. Actual Factor IX potency for 500 unit vial ranges from 400-620 units/vial and for 1000 unit vial ranges from 800-1240 units/vial.
  - Approved for use in adults and children

Von Willebrand Disease (vWD)

- Humate-P® (CSL Behring)
  - Plasma derived product; contains vWF and Factor VIII
  - Available in single dose vials containing 600 IU vWF:RCo & 250 IU FVIII, 1200 IU vWF:RCo & 500 IU FVIII, or 2400 IU vWF:RCo vWF & 1000 IU FVIII.
    Average ratio of vWF:RCo to FVIII is 2.4:1 per vial.
  - Approved for use in adults and children
- Wilate® (Octapharma)
  - Plasma derived product; contains vWF and Factor VIII
  - Available in single use vials containing 500 IU vWF:RCo and 500 IU FVIII (5mL) or 1000 IU vWF:RCo and 1000 IU FVIII (10mL). Average ratio of vWF:FVIII is 1:1 per vial.
  - Approved for use in children and adults
- Vonvendi® (Takeda)
  - Recombinant product; contains *only* vWF

- Available in single use vials containing either 650 or 1300 IU vWF:RCo
- Approved for use in adults

Bleeding Disorders with Inhibitors:

Patients with INHERITED Hemophilia A or B and Inhibitors to Factor VIII or Factor IX

- FEIBA (Takeda) - Anti-inhibitor coagulant complex
  - Also known as Activated Prothrombin Complex Concentrate [aPCC]
  - Plasma derived product containing 4 factors (Factors II, VII, IX, and X). Of these, only factor VII is mostly the activated form.
  - Available as single use vials labeled with the amount of factor VIII inhibitor bypassing activity in units. Nominal units per vial include 500 (Factor VIII potency 350-650 units), 1000 (Factor VIII potency-700-1300 units) or 2500 (Factor VIII potency 1750-3250 units).
  - Approved for adults or children over age 6 with hemophilia
  - Contraindicated for use in patients with DIC (disseminated intravascular coagulation) and acute thrombosis or embolism (including myocardial infarction).
- Novoseven®RT (Novo Nordisk) – Recombinant Activated Factor VII Concentrate [rFVIIa]
  - Recombinant product
  - Available in single-dose vials containing either 1, 2, 5, or 8 mg recombinant coagulation factor VIIa
  - Approved for use in adults and children

Patients with ACQUIRED Hemophilia and Factor VIII Inhibitors[1]

- Novoseven®RT (Novo Nordisk) – Recombinant Activated Factor VII Concentrate [rFVIIa]
  - Recombinant product
  - Available in single-dose vials containing either 1, 2, 5, or 8 mg recombinant coagulation factor VIIa
  - Approved for use in adults and children
- Obizur (Baxalta US) – Recombinant Factor VIII, Porcine Sequence
  - Recombinant DNA-derived product, porcine sequence
  - Indicated for on-demand treatment and control of bleeding in patients with acquired hemophilia A
  - Available in single use vial containing a nominal dose of 500 units
  - Approved for use in adults

Other Rare Bleeding Disorders:

Antithrombin Deficiency

- Thrombate III (Grifols)
  - Plasma derived product
  - Available in single use vials containing approximately 500 units antithrombin
  - Approved for use in adults

Fibrinogen Deficiency

- RiaSTAP® (CSL Behring) – Fibrinogen concentrate

  - Plasma derived product
  - Available in single use vials containing approximately 900-1300 mg fibrinogen
  - Approved for use in adults
  - Not indicated for dysfibrinogenemia due to risk for increased thrombosis.
- Fibryga® (Octapharma) – Fibrinogen concentrate
  - Plasma derived product
  - Available in single use vials containing approximately 1000 mg fibrinogen in a prepackaged kit with filter and transfer device
  - Approved for use in adults and adolescents
  - Not indicated for dysfibrinogenemia due to risk for increased thrombosis.
- Both RiaSTAP® and Fibyga® have been used off-label for acquired hypofibrinogenemia in patients with massive bleeding associated with cardiac surgery, trauma, and obstetric hemorrhage. [2-4]

Hereditary Angioedema

- Berinert® (CSL Behring) – C1 Esterase Inhibitor
  - Plasma derived product
  - Available in single use vials containing approximately 500 IU of C1 esterase inhibitor
  - Approved for use in adults and adolescents

Protein C Deficiency

- Ceprotin® (Shire) – Protein C
  - Plasma derived product
  - Available in single use vials containing either 500 IU or 1000 IU protein C
  - For use in severe protein C deficiency [protein C activity level <1 IU/dL (normal range 65-135 IU/dL)]
  - Approved for use in adults and pediatric patients

Recommendations for emergency management of patients with hemophilia or other bleeding disorders by the National Hemophilia Foundation[5] are summarized below.

Triage:

1) Individuals with bleeding disorders should be triaged urgently as delays in administering appropriate therapy, such as infusion of factor concentrate, can significantly affect morbidity and mortality.
2) Consultation with the patient's primary provider of bleeding disorder care, in most cases a hematologist, is strongly advised. If this provider is unavailable, consultation with a bleeding disorders provider from the closest hemophilia treatment center is recommended. Administration of clotting factor replacement should not be delayed while waiting for a consultation.

Assessment:

1) Treatment for a suspected bleeding episode is based on clinical history. Physical exam findings may be normal in the early phases of most bleeding episodes associated with an

underlying bleeding disorder. Spontaneous bleeding is common in those with severe disease (baseline factor levels <1%). When in doubt, administer clotting factor replacement therapy immediately.

- The dose and frequency of factor delivery is based upon the half-life of the product, intravascular volume of distribution, and desired clotting factor activity.
- One international unit (IU) per body weight (kg) of product infused will generally raise the factor level by 1 to 2 IU/dL (or 1-2%).
- Refer to FDA-approved package inserts for exact recovery and dose calculation formula.

2) Urgent treatment decisions should be based on the suspicion of a bleeding-related problem, not the documentation of one.
3) If the patient or the parent of a patient suspects that occult bleeding is occurring, administer clotting factor replacement. Patients often are instructed to carry medications with them for rapid treatment as advised by their hematologist.

Acquired Disorders including Hypocoagulability due to Anticoagulation

Management of Patients with Supratherapeutic INR

Warfarin Reversal:

- Warfarin mechanism of action: inhibit the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X and the anticoagulant proteins C and S. Half-life: 20 to 60 hours (mean ~ 40 hours). Refer to package insert.
- Therapeutic management of hypocoagulability due to warfarin is based on the INR and presence of active bleeding. Refer to Table 1.

Table 1: Suggested Management of Supratherapeutic INR[6,7]

INR and Clinical Situation	Recommended Action	Comments
≥ 5 to < 10 No bleeding or minor or insignificant bleeding	• Reduce or omit 1-2 doses of Warfarin	
≥ 10 No bleeding or minor or insignificant bleeding	• Omit at least 2 doses of Warfarin • Vitamin K 1-2.5 mg PO	• If prompt reversal of Warfarin (within 2-6 hours) is needed, consider administration of Vitamin K 2.5-5 mg IV.
Any INR and major/**life threatening** bleeding	• Hold Warfarin • Administer 4F-PCC (Kcentra®) 1000-1500 units IV once (based on severity of bleed), and • Vitamin K (5-10 mg) slow IV infusion over 30-60 minutes	• *Repeat INR testing is not required unless the patient experiences clinical changes in status related to bleeding.* • Do not use Kcentra® in patients who have heparin-induced thrombocytopenia (HIT) or a history of HIT (Kcentra® contains 8-40 units of heparin). • PCC is recommended over plasma for rapid correction of warfarin-related bleeding unless PCC is unavailable.

4-Factor Prothrombin Complex Concentrate (4-F PCC) (Kcentra®)

Indications:

- Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding or need for urgent surgery or other invasive procedure.

Dosing:

- Kcentra® (CSL Behring) is available as a single-use vial containing inactive forms of four coagulation factors (Factor II, VII, IX and X) and antithrombotic Proteins C and S, as a lyophilized concentrate.
- Dosing for warfarin-reversal may be based on either one of the following:
  - Fixed dosing of 1000-1500 units, which is found to be safe, effective, and more efficient for rapid reversal of Warfarin anticoagulation [7-9]
  - Calculation based on INR result at presentation and body weight; typical dose for INR >6 is 50 units/kg body weight. Refer to package insert.

Comments:

- Four-factor PCC should be used with caution in patients with chronic or advanced liver disease, and if used, conservative dosing applied since thromboembolic events have been identified.[10-11] Patients with end stage liver disease have deficiency in procoagulants **as well as** anticoagulants. PCC contains protein C and protein S, but little to no anti-thrombin (refer to package insert). PT/INR reversal and hemostasis correction with 4F-PCC in patients with liver disease cannot be expected to occur to the same extent as in patients treated with VKAs.[10] In patients with liver disease it is best to use multiple coagulation assays, including whole blood viscoelastic tests of hemostasis, to help assess coagulation status.[12]
- Non-FDA approved use should be considered with caution and may include:
  - Protein S deficiency where no concentrate is available
  - Reversal of direct oral anticoagulants (DOAC) such as rivaroxaban, apixaban or edoxaban (see Table 2 below)
  - Treatment of other acquired factor deficiencies and trauma-induced coagulopathy

Management of Patients on Direct Oral Anticoagulant (DOAC) Medication

Reversal Agents – See Table 2

- Typically used in the setting of clinically relevant major or life-threatening bleeding or for emergent/urgent surgery or procedures [7, 13-14] Refer to institution's pharmacy policies/procedures for reversal agent availability and dosing. This information is for educational purpose only.

Comments:

- If specific reversal agent is not available, 4F-PCC (i.e., 2000 units) may be an effective alternative for treatment of major bleeding associated with Factor Xa inhibitors. [7,13]
- Plasma will **NOT** reverse the effects of these direct oral anticoagulant medications (DOAC).

Table 2: Direct Oral Anticoagulant Reversal Agents

DOAC	Reversal Agent	Recommended Actions
Factor Xa Inhibitors: Rivaroxaban (Xarelto) Apixaban (Eliquis) Edoxapan (Savaysa)	Andexanet Alfa (Alexion Pharmaceuticals, Inc) May consider use of 4-factor PCC (Kcentra®)	• **Stop DOAC** • Ongoing monitoring of coagulation lab results and bleeding • Compression and/or local control of bleeding source • Administer activated charcoal if ingested within the prior 2 hours • Consider use of tranexamic acid (avoid if hematuria)
Factor IIa inhibitor: Dabigatran (Pradaxa)	Praxbind (Idarucizumab) (Boehringer Ingelheim Pharmaceuticals, Inc.)	

References:

1. Tiede A, Collins P, Knoebl P, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. *Haematologica*. 2020;105(7):1791-1801. https://www.haematologica.org/article/view/9931
2. National Advisory Committee on Blood and Blood Products – NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia. V: 20210126. Available at: https://www.nacblood.ca/resources/guidelines/downloads/2021%20FC%20Statement%20Update20210310.pdf)
3. Levy JH, Goodnough LT. How I use fibrinogen replacement therapy in acquired bleeding. *Blood* 2015; 125(9):1387-1393. https://doi.org/10.1182/blood-2014-08-552000
4. Cushing MM, Haas T, Karkouti K, Callum J. Which is the preferred blood product for fibrinogen replacement in the bleeding patient with acquired hypofibrinogenemia - cryoprecipitate or fibrinogen concentrate? *Transfusion* 2020; 60:S17-S23. https://doi.org/10.1111/trf.15614
5. MASAC Document 257 - Guidelines for Emergency Department Management of Individuals with Hemophilia and Other Bleeding Disorders. December 5, 2019. Available at: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/Guidelines-for-Emergency-Department-Management-of-Individuals-with-Hemophilia-and-Other-Bleeding-Disorders
6. Holbrook A, Shulman S, Witt DM et al. Evidence-based management of anticoagulant therapy. *CHEST* 2021;14(2): e152S - e184S. doi: 10.1378/chest.11-2295
7. Tomaselli GF (Chair), Mahaffey KW (Vice chair). 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *J Am Coll Cardiol* 2020; 76(5): 594-622. https://doi.org/10.1016/j.jacc.2020.04.053
8. Rhoney DH, Chester KW, Darsey DA. Optimal dosage and administration practices for vitamin K antagonist reversal with 4-factor prothrombin complex concentrate. *Clin Appl Thromb Hemost*. 2020 Jan-Dec;26:1076029620947474. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7573754/
9. Jansma B, Montgomery J, Dietrich S, et al. Emergent warfarin reversal with fixed-dose 4-factor prothrombin complex concentrate. *Annals of Pharmacotherapy*. 2020;54(11):1090–1095. https://pubmed.ncbi.nlm.nih.gov/32418445/
10. Huang, W-T, Cang WC, Derry KL et al. Four-factor prothrombin complex concentrate for coagulopathy reversal in patients with liver disease. *Clin Appl Thromb Hemost* 2017;23(8):1028-1035. https://journals.sagepub.com/doi/10.1177/1076029616668406
11. Drebes A., de Vos M., Gill S., et al. Prothrombin complex concentrates for coagulopathy in liver disease: single-center, clinical experience in 105 patients. *Hepatology Communications*. 2019;3:513-524. https://doi.org/10.1002/hep4.1293
12. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. *Gastroenterology* 2019;157:34-43. https://www.sciencedirect.com/science/article/pii/S001650851935694X?via%3Dihub
13. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from Anticoagulation Forum. *Am J Hematology* 2019;94(6):697-709. https://doi.org/10.1002/ajh.25475
14. Desaia NR, Cornutt D. Reversal agents for direct oral anticoagulants: considerations for hospital physicians and intensivists. *Hospital Practice*. 2019;47(3):113-122. https://doi.org/10.1080/21548331.2019.1643728

Additional Resources:

- National Hemophilia Foundation https://www.hemophilia.org/
- National Organization of Rare Diseases https://rarediseases.org/rare-diseases/acquired-hemophilia/
- Treat the Bleed (website) Canada https://treatthebleed.org/

Medication Package Inserts

1. Kogenate®FS (Bayer) https://www.kogenatefs.com/home/prescribing-information
2. Hemofil M (Takeda) https://www.shirecontent.com/PI/PDFs/HEMOFILM_USA_ENG.pdf
3. ELOCTATE (Bioverativ Therapeutics) https://products.sanofi.us/Eloctate/Eloctate.pdf
4. JIVI® (Bayer HealthCare LLC) https://labeling.bayerhealthcare.com/html/products/pi/Jivi_PI.pdf
5. DDAVP (Desmopressin) Injection https://products.sanofi.us/ddavp_iv/ddavp_iv.pdf
6. BeneFIX® (Pfizer) http://labeling.pfizer.com/showlabeling.aspx?id=492
7. Rixubis® (Shire) https://www.shirecontent.com/PI/PDFs/RIXUBIS_USA_ENG.pdf
8. Alprobix (Bioverativ Therapeutics/Sanofi US) https://products.sanofi.us/Alprolix/alprolix.html
9. Kcentra® package insert. CSL Behring, Marburg Germany, October 2018. https://labeling.cslbehring.com/PI/US/Kcentra/EN/Kcentra-Prescribing-Information.pdf
10. Humate-P® (CSL Behring) https://labeling.cslbehring.com/PI/US/Humate-P/EN/Humate-P-Prescribing-Information.pdf
11. Wilate® (Octapharma) https://www.wilateusa.com/wp-content/uploads/2019/10/20190923_pil_18x_USA_26.pdf
12. Vonvendi® (Takeda) https://www.shirecontent.com/PI/PDFs/VONVENDI_USA_ENG.pdf
13. FEIBA (Takeda) https://www.shirecontent.com/PI/PDFs/FEIBA_USA_ENG.pdf
14. NovoSeven®RT https://www.novo-pi.com/novosevenrt.pdf
15. Obizur (Baxalta US) https://www.shirecontent.com/PI/PDFs/OBIZUR_USA_ENG.pdf
16. Thrombate III (Grifols) https://www.thrombate.com/documents/51038104/51038282/THROMBATE+-+PI/fce61957-3696-4aff-b6c6-b09d4225cae3
17. RiaSTAP® (CSL Behring) http://cslbehring.vo.llnwd.net/o33/u/central/PI/US/RiaSTAP/EN/RiaSTAP-Prescribing-Information.pdf
18. Fibryga® (Octapharma) https://www.fibrygausa.com/why-fibryga/#hcp Package insert at: https://www.fibrygausa.com/wp-content/uploads/2021/03/20201222_pil_347_11.07_US_en.pdf
19. C1 esterase inhibitor, Berinert® (CSL Behring) https://labeling.cslbehring.com/PI/US/Berinert/EN/Berinert-Prescribing-Information.pdf
20. Protein C, Ceprotin® (Shire) https://www.ceprotin.com/Contents/PDFs/ceprotinhcp_usa_eng.pdf
21. Bristol-Myers Squibb Company. Coumadin (warfarin sodium) tablets package insert. Princeton, NJ: Bristol-Myers Squibb Company; December 2019.
22. Andexanet Alfa (Alexion Pharmaceuticals, Inc.) https://andexxa.com/
23. Praxbind (Idarucizumab) (Boehringer Ingelheim Pharmaceuticals, Inc.) https://www.praxbind.com/idarucizumab/what-is-praxbind Package insert at: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf