

# BLOOD BULLETIN

VOL. 5, NO. 2      DECEMBER 2002

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## COAGULATION PRODUCTS USED IN THE TREATMENT OF HEMOSTATIC DISORDERS

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**Introduction.** Several new coagulation concentrates developed over the last few years continue the trend toward higher specificity and greater safety. This edition of *Blood Bulletin* provides a brief overview of the composition, indications, and dosing guidelines of currently-licensed products.

**Antihemophilic Factor (FVIII) Products.** Available preparations include recombinant and plasma-derived monoclonal and intermediate purity factor VIII (See Table I). The plasma-derived products are further subjected to viral inactivation procedures, which include heat or solvent detergent treatment. Issues surrounding both known<sup>1</sup> and potential<sup>2</sup> infectious agents have fostered increasing use of recombinant products. "Second generation" recombinant products are devoid of animal proteins and/or human serum albumin stabilizing agents present in previous recombinant products.<sup>3</sup>

Factor VIII concentrates are indicated for the treatment or prevention of bleeding in patients with hemophilia A. Patients with moderate (factor VIII:C levels at 1-5%) or severe deficiency (factor VIII:C levels at <1%) generally require factor replacement for treatment of hemorrhage and surgery. Minor hemorrhages, such as mild hemarthroses, soft tissue hemorrhage, dental bleeding, and epistaxis usually require factor replacement to 30-50% of normal levels (15 to 25 units/kg). Major hemorrhages including head trauma, retroperitoneal hemorrhage, and surgical procedures require factor infusion initially to 80 to 100% of normal, with repeat dosing based on the half-life of FVIII, q every 8-12 hours, over a period of 7-14 days, e.g., 50 units/kg initially followed by 25 units/kg q every 8-12 hours. Dosing adequacy should be checked by regular monitoring of factor VIII levels. Factor VIII inhibitors may be detected by a poor response to treatment.

**Von Willebrand Factor (vWF) containing products.** Although several intermediate purity factor VIII products contain high molecular weight multimers of vWF,<sup>4</sup> only one antihemophilic factor/vWF complex is licensed for use in the management of von Willebrand Disease (vWD). Efficacy has been demonstrated in patients with various vWD subtypes, including Type I, IIA, IIB, and III. Although routinely used for surgery, controlled clinical trials have not been performed in this setting.

Recommended dosing is that which will raise the level of vWF to between 50 and 100% of normal depending upon the severity of the hemorrhage or need for surgical procedure. The dose may be repeated at 8 to 12 hour intervals to maintain vWF levels of at least 50% of normal, for 3 to 10 days depending upon the nature and/or risk of bleeding. Monitoring of therapeutic levels is advised.<sup>4,5</sup>

**Factor IX Concentrates.** Factor IX concentrates are available as recombinant or plasma derived products. Only recombinant or high purity plasma derived factor IX products are recommended for the treatment of patients with hemophilia B (factor IX deficiency). Minor hemorrhages may be treated to achieve 20-30% levels of factor IX. Moderate hemorrhages are treated by achieving 25 to 50% level of factor IX and major hemorrhages are maintained be-

**SUMMARY:** Specific agents derived from blood (either as plasma products or as recombinant proteins) have superseded the use of standard blood components for a growing number of clinical indications. Purified FVIII and IX products with improved safety are used to treat patients with hemophilia. Von Willebrand factor-containing concentrates and viral inactivated-fibrinogen (fibrin sealant) are now available for use in place of cryoprecipitate in the treatment of vWD and localized surgical bleeding, respectively.

tween 50 and 100% levels, for 7-14 days. Because of its long half-life, dosing generally is at 12 to 24 hour intervals; the recombinant product currently available has a lower recovery than plasma derived products in many patients.

**Factor IX Complex Concentrates.** Formerly known as Prothrombin Complex Concentrates, these products are mixtures of Vitamin K dependent coagulation factors II, VII, IX, and X that have been useful in the treatment of patients with inhibitors of factor VIII and IX. It is believed that the presence of activated factors—in particular VIIa, IXa, and Xa—generates sufficient thrombin in the absence of factor VIII or IX to achieve hemostasis. Two products have higher levels of activated coagulation factors: Autoplex® and FEIBA.<sup>6</sup> Clinical studies between activated concentrate and a non-activated factor IX complex concentrate showed no differences in efficacy in treating joint hemorrhage in hemophiliacs with a factor VIII inhibitor.<sup>7</sup> However, due to the risk of thrombosis, some reserve the use of the activated components for more serious hemorrhages or hemorrhages that have failed to respond to non-activated factor IX concentrates. In both hemophiliacs with inhibitors and in those who develop spontaneous anti-factor VIII antibodies, establishment of a normal level of factor VIII is considered the best approach if feasible. This approach is practical in only the small percentage of patients who have a low titer anti-VIII level (<5 to 10 Bethesda units/ml). In such patients, it may be possible to achieve hemostasis by infusing FVIII (human or porcine<sup>8</sup>) at high doses. Strategies to bypass the inhibitor are necessary in high titer inhibitor patients. The dose of low-purity or activated factor IX concentrates is 50 to 100 units/kg with a maximum single dose of 100 units/kg and 200 units/kg/day to minimize thrombotic complications. Patients considered to be at higher risk of thrombosis include those with DIC, liver dysfunction or intensive or prolonged infusion.<sup>9</sup>

**Recombinant Factor VIIa** acts in concert with tissue factor to initiate the extrinsic coagulation system leading to activation of X to Xa, IX to IXa, and conversion of prothrombin to thrombin. Pharmacologic levels may also directly activate X to Xa on the platelet surface, leading to enhanced thrombin generation and a fully stabilized fibrin plug. Factor VIIa was licensed in 1999 for

Table I. Current US-licensed products by category

Product Type	Name	Manufacturer	Notes
Recombinant FVIII	Recombinate	Baxter	Albumin stabilizer
	Kogenate FS	Bayer	Sugar stabilizer
	Bioclata	Baxter (Dist. by Aventis)	Albumin stabilizer
	Helixate	Bayer (Dist. by Aventis)	Sugar stabilizer
	Refacto	Wyeth	B-domain deleted; Sugar stabilizer
Monoclonal Plasma-derived FVIII	Hemofil M	Baxter	IC,SD
	Monarc-M	Baxter (Dist. by Am Red Cross)	IC,SD, volunteer donor plasma
	Monoclate P	Aventis	IC, pasteurized
Intermediate Purity Plasma-derived FVIII	Alphanate SD	Alpha Therapeutics	AC, SD, HT (80°/72 hr); Contains vWF <sup>5</sup>
	Humate-P	Aventis	Licensed for use in vWD patients
	Koate HP, Koate DVI	Bayer	HP-SD; DVI- SD, HT (80°/72 hr); contains some vWF <sup>5</sup>
	Hyate-C		
Recombinant FIX	Benefix	Genetics Institute (Dist. by Wyeth-Ayerst)	Animal protein & albumin free
Monoclonal Plasma-derived FIX	AlphaNine SD	Alpha Therapeutics	SD, nanofiltration
	Mononine	Aventis	IC, ultrafiltration
Anti-Inhibitor Coagulant Complex Concentrates	FEIBA VH	Baxter	VH
	Autoplex T	Baxter (Dist. by Nabi)	HT, 60°/144 hr.
	Konyne 80	Bayer	HT, 80°/72 hr.
	Proplex T	Baxter	HT, 60°/144 hr.
			} not currently available**
Recombinant FVIIa	NovoSeven	Novo Nordisk	No added animal protein or albumin ( <i>trace levels of murine monoclonal antibody from purification</i> )
Fibrin Sealant	Tisseel VH	Baxter	Contains bovine aprotinin and human thrombin and fibrinogen

AC Affinity chromatography; DVI Double viral inactivation; HP High purity; HT Dry heat treated; IC Immunoaffinity chromatography; Pasteurized 60°/10 hrs.; SD Solvent detergent treated; VH Vapor heated; vWF von Willebrand Factor

\*\* Note: Baxter distributes a low purity factor IX complex (that contains factors X and prothrombin) as *Bebulin*, VH (prepared in Austria, formerly by Immuno); its use is primarily as a less expensive alternative for hemophilia; it is not particularly effective when inhibitors are present. It has a higher thrombotic risk, however, than the more purified factor IX concentrates.

treatment of hemophilia A and B patients with inhibitors, and is also used in the treatment of patients with acquired inhibitors to factor VIII and congenital factor VII deficiency. Reported efficacy in the management of hemophilic bleeding also extends to elective surgery, previously considered contraindicated in hemophilia patients with inhibitors.<sup>10</sup> The minimal effective dose has not been established. The initial recommended dose is 90 mcg/kg every two hours until cessation of hemorrhage.<sup>11</sup> Generally, three doses are given and clinical assessment is performed. Once hemostasis is achieved, a tapering schedule with increasing intervals of 3-4 hours may be considered over 24 hours. The dose schedule for surgery is more intensive and requires continuous coverage for three to five days. If the 90 mcg/kg dose fails to have a hemostatic effect, some centers try a higher dose, up to 160 mcg/kg.

**Fibrin Sealant.** Fibrin sealants are used for topical hemostasis and comprise two major components: fibrinogen and thrombin (plus calcium and usually an antifibrinolytic agent). One preparation is licensed in the United States as a freeze-dried product made from vapor heated pooled human plasma. A recent meta-analysis of 12 clinical trials reported overall efficacy of a 60% reduction in the use of allogeneic blood transfusion, however, reduction in average blood loss per case was only approximately 150 mls.<sup>12</sup>

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