

Implementing guidelines for the institutional use of factor VIIa (recombinant): A multidisciplinary solution

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Problem

Recombinant activated factor seven (VIIa) is a vitamin K-dependent glycoprotein that is structurally similar to human plasma-derived factor VIIa. It has received approval from the Food and Drug Administration (FDA) for the treatment of bleeding episodes in patients with hemophilia A or B who have developed inhibitors to factor VIII or factor IX, respectively.¹ It promotes hemostasis by activating the coagulation cascade. Complexing with tissue factor at the site of vascular injury, recombinant factor VIIa cleaves factor X to the enzyme-activated factor X. Factor X promotes the conversion of prothrombin to thrombin and of fibrinogen to fibrin, leading to the formation of a hemostatic plug.^{2,3}

Factor VIIa (recombinant) has been primarily used in the treatment of bleeding episodes in hemophilic patients with inhibitors to factor VIII or IX and patients with acquired hemophilia due to autoantibodies. The current recommended dose of factor VIIa (recombinant) in the treatment of bleeding episodes in these patients is 90 µg/kg i.v.¹ In this population, factor VIIa (recombinant) has been associated with adverse thromboembolic events, including myocardial

infarction, cerebrovascular infarct, venous thrombosis, and disseminated intravascular coagulopathy (DIC).^{1,4}

However, the medical literature provides anecdotal reports of factor VIIa (recombinant) use for a growing list of unlabeled indications, including the reversal of warfarin toxicity,⁵ treatment of pediatric patients with coagulation dysfunction,⁶ and treatment of patients with coagulation disorders caused by hepatic disease.⁷ One randomized controlled trial found that factor VIIa (recombinant) reduced blood loss and blood-product requirements in patients undergoing high-risk surgical procedures,⁸ and another revealed that factor VIIa (recombinant) controlled

the bleeding associated with intracerebral hemorrhage (ICH).⁹ Doses for the treatment of uncontrolled hemorrhage in other clinical settings have varied from 15 to 180 µg/kg i.v.²

Our institution, the University of Virginia Health System (UVHS), added factor VIIa (recombinant) to its formulary on August 27, 1999. Informal institutional guidelines restricted the use of factor VIIa (recombinant) to patients with hemophilia A or B with inhibitors, patients with autoimmune antibodies to factor VIII, and patients with bleeding associated with liver disease. These guidelines were developed by the hematology–oncology service to identify the clinical conditions for which patients could receive factor VIIa (recombinant). The pharmacy and therapeutics (P&T) committee did not approve these informal guidelines. The informal guidelines also allowed the use of factor VIIa (recombinant) for the treatment of intractable bleeding, central nervous system bleeding, and warfarin reversal. However, a formal hematology consultation and documentation of the specific risks and benefits in the patient's medical record were required for the unlabeled indications. The initial gatekeeper was a hema-

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tologist who had significant experience with factor VIIa (recombinant). The hematologist or her designated hematology fellows (not assigned through a formal P&T committee process) approved or disapproved the release of the drug for all consultations. However, the approval process became overwhelming for the hematologist because of the increased demand for factor VIIa (recombinant) for unlabeled indications.

The unlabeled uses of factor VIIa (recombinant) are constrained by high costs and limited clinical efficacy data. Currently, there are no national guidelines for the unlabeled indications of factor VIIa (recombinant); before April 2005, our institution did not have formal prescribing guidelines for the agent. Inappropriate use of the anticoagulation factor may negatively affect drug expenditures. Hoffman and colleagues¹⁰ identified factor VIIa (recombinant) as a major contributor to escalating pharmacy drug budgets in many of today's major academic medical centers. During the 2004 fiscal year, UVHS spent approximately \$970,000 on this agent alone.

We conducted a project at UVHS to determine our usage pattern of factor VIIa (recombinant) and establish formal prescribing guidelines for the use of the drug within the institution.

Analysis and resolution

UVHS is a tertiary care academic medical center located in Charlottesville, Virginia. The medical center has approximately 650 licensed beds and is a state-designated level 1 trauma center. The medical center is an integrated network of primary and specialty care services and serves as a training center for the university's colleges of medicine and nursing and an experiential site for students from the Medical College of Virginia–Virginia Commonwealth University and the Shenandoah School of Pharmacy.

Data collection. Our first step was to conduct a prospective medication-use evaluation (MUE). Inpatients receiving factor VIIa (recombinant) between August and October 2004 were the focus of the MUE. Patients were identified through daily computer-generated printouts. Information collected included the patient's weight, indication for factor VIIa (recombinant) use, dose, administration schedule, contraindications and precautions for factor VIIa (recombinant) use, and data for monitoring safety and efficacy outcomes.

A total of 12 patients were identified as receiving factor VIIa (recombinant) during the three-month MUE period (Table 1). All but 1 patient were taking the drug for an unlabeled indication. Seven patients had liver disease (hepatitis B, hepatitis C, fulminant hepatic failure [FHF], alcoholic cirrhosis) and received factor VIIa (recombinant) to stop or prevent bleeding before or after an inpatient procedure. Before administration of factor VIIa (recombinant), all patients received blood products or vitamin K to facilitate hemostasis.

According to the initial informal guidelines, 9 patients had known precautions for using factor VIIa (recombinant), 2 of whom had contraindications for using the agent. However, these patients still received factor VIIa (recombinant). There were occasions when a compelling request by other physicians allowed use of factor VIIa (recombinant) because the potential benefits exceeded the risks. The precautions, as described in the initial guidelines, included crush injury, DIC, septicemia, and signs of coagulation system activation or thrombosis (e.g., thromboembolic disease, pulmonary emboli, elevated International Normalized Ratio [INR], prolonged partial thromboplastin time). Both patients with contraindications had DIC. Seven patients had an INR of <1.8, and 1 patient had a fibrinogen level

of <120 mg/dL, both of which were precautions against using the medication. These latter precautions were set forth by the hematologist and were based on her clinical experience. Repeat administration was required for 8 patients, bleeding stopped in 10 patients, and 6 patients died from reasons other than bleeding. Of the patients who required repeat doses, some received higher repeat doses than the initial dose given.

Cost–benefit analysis. Using the MUE data, a cost–benefit analysis was conducted to analyze the cost per bleeding episode stopped. The associated costs for each of the 12 patients during the MUE period are listed in Table 1. These costs were based on contract prices obtained by the UVHS pharmacy department. During the three-month MUE, factor VIIa (recombinant) costs to the pharmacy department were \$63,240 for unlabeled indications, compared with \$170,340 for the FDA-approved indications. The cost–benefit analysis revealed that the average costs per bleeding episode stopped in patients with factor deficiency, patients with liver disease, and patients undergoing neurosurgery were \$170,340, \$9,996, and \$3,315, respectively.

Presentation to the P&T committee. These data were presented to the P&T committee, which recommended that a multidisciplinary work group establish formal institutional guidelines for using factor VIIa (recombinant). The work group consisted of physicians and clinical pharmacists from hematology, hepatology, pediatrics, neurosurgery, internal medicine, and critical care. The MUE data were then presented to the work group for review. Discussion ensued regarding the increase in unlabeled uses and the associated costs of factor VIIa (recombinant). The group recognized the need to develop indication-specific guidelines for the FDA-approved and unlabeled indications. The group also recommended expanding the formal

Table 1.
Cost-Benefit Analysis for Using Factor VIIa (Recombinant)

Patient	Indication ^a	No. Repeat Doses	Cost ^b	Outcome
1	Subarachnoid hemorrhage	0	\$2,040	Bleeding stopped
2	Liver disease (undergoing ICP monitor placement)	2	\$21,420	Bleeding stopped
3	Liver disease (removal of central line)	0	\$4,080	Bleeding continued
4	Liver disease (undergoing ICP monitor placement)	1	\$3,060	Bleeding stopped
5	Intracerebral hemorrhage	0	\$4,080	Bleeding stopped
6	Liver disease (TIPS replacement)	2	\$8,160	Bleeding continued
7	Thrombocytopenia secondary to liver disease (emergent neurosurgery)	1	\$2,040	Bleeding stopped
8	Liver disease (tracheotomy tube placement)	1	\$3,060	Bleeding stopped
9	Liver disease (subdural hematoma evacuation)	1	\$8,160	Bleeding stopped
10	Factor VIII deficiency	30	\$170,340	Bleeding stopped
11	Subdural hemorrhage	0	\$1,020	Bleeding stopped
12	ICP monitor placement	1	\$6,120	Bleeding stopped

^aICP = intracranial pressure, TIPS = transjugular intrahepatic portosystemic shunt.

^bCosts were based on contract prices obtained by the department of pharmacy.

approval process from a single service area to those clinical areas with the greatest expertise in the use of factor VIIa (recombinant) for subsequent prescribing, dispensing, and administration of factor VIIa (recombinant) within UVHS. This plan ensured appropriate medication use while reducing costs and minimizing potential adverse events without compromising therapy for those patients requiring the drug.

Development of formal institutional guidelines. The P&T committee asked the work group to develop adult and pediatric indication-specific guidelines for the FDA-approved and unlabeled indications of factor VIIa (recombinant) using guidance from current literature and clinical practice. Guidelines were developed for the treatment of patients with hemophilia with inhibitors, acquired (autoimmune) factor VIII antibodies, warfarin toxicity, ICH, liver disease with uncontrolled variceal bleeding or postprocedure bleeding, and FHF requiring prophylactic therapy for the placement of an intracranial pressure (ICP) monitor. Guidelines were also developed for high-risk patients requiring thoracentesis. Specific details on dosing and monitoring parameters for each indication were defined within

the guidelines. The guidelines were presented to the P&T committee, approved, and implemented hospitalwide in May 2005. The guidelines are provided in Appendix A.

The formal guidelines promoted a shared gatekeeping responsibility and a new procedure for ordering, dispensing, and administering the product to maximize compliance and ensure cost-effective use of factor VIIa (recombinant). Prior authorization by a designated attending physician (or a selected fellow in the absence of an attending physician) from the appropriate service is required for the respective indications. A compiled list identifying the names of physicians who can approve factor VIIa (recombinant) use was disseminated to the medical staff and pharmacy department.

A special form was developed to assist the requesting physician with collecting the necessary information before discussing the patient with the respective approving physician. The requesting physician completes the form to expedite the retrieval of information necessary for the approving physician. The form is a carbon copy, with one copy remaining in the patient's medical record and the other sent to the pharmacy for record-keeping purposes.

Implementation of formal guidelines, staff development, and education. The responsibility of the pharmacy department was to disseminate the guidelines and educate the nursing and physician staffs. The updated guidelines were disseminated throughout the institution via several methods. The screens of the computerized prescriber-order-entry system were updated by the pharmacy department to inform physicians and pharmacists about the prescribing information within the new guidelines. The updated screens reminded physicians about the specific indications and parameters for using factor VIIa (recombinant). Detailed pocket-sized reference cards that described the new guidelines and the new procedures for requesting factor VIIa (recombinant) were developed by the pharmacy department. The cards were distributed hospitalwide. In addition, the new guidelines and procedures for obtaining factor VIIa (recombinant) were presented by pharmacy personnel during monthly meetings of the pharmacy department staff and the nursing and pharmacy committee. The guidelines were also posted on the drug information intranet. The respective gatekeepers were responsible for developing an intranet-based competency lesson

for mandatory completion by all medical interns, residents, fellows, and attending physicians. The gatekeepers also presented the information during medical grand rounds and hematology–oncology grand rounds in an attempt to educate as many physicians as possible.

A subsequent MUE was conducted to evaluate adherence to the formal P&T-approved guidelines. The MUE included patients admitted from June 1 to November 11, 2005, who received factor VIIa (recombinant). In 18 of 19 patients, the appropriate gatekeeper physician approved the medication. Factor VIIa (recombinant) was used in 17 patients (89%) for an indication within the formal guidelines, and 2 (11%) received recombinant factor VIIa outside of the guidelines. The primary indication for factor VIIa (recombinant) use was to correct coagulopathy before an emergency procedure, particularly before ICP monitor placement. The results of this follow-up MUE indicate that factor VIIa (recombinant) use adhered to the formal guidelines for the majority of patients.

The implementation process had minimal impact on pharmacy workload. Though additional time was required for surveillance to ensure that the physicians ordering factor VIIa (recombinant) were following the guidelines, the time spent on this task was negligible.

Discussion

Given the observational nature of published information for FDA-approved and unlabeled indications, there may be great variability in practice patterns for factor VIIa (recombinant) use. To maximize clinical benefits while minimizing risks and expenditures, our institutional goals were to assess factor VIIa (recombinant) usage patterns, prepare guidelines for use, and develop an implementation process for these guidelines.

According to the most recent guidelines published by the American Society of Health-System Pharmacists, a key ingredient in MUE is the need for a multifaceted approach to effectively improve the medication process.¹¹ Paramount to the successes of any patient care MUE program is the need for collaborative efforts and institutional support among physicians, pharmacists, and administrators.¹¹ However, MUE results by themselves are merely observations. In order to affect medication-use patterns, collaborative efforts are needed to develop guidelines, educate staff, and implement change.

Despite the never-ending challenges faced by pharmacy in today's dynamic health care system, the development of processes for monitoring and evaluating drug therapy expenditures can play a critical role to both clinical and nonclinical decision-makers within a given health system.¹⁰ The ability to collaborate within the health care system with other stakeholders for select therapies can reduce barriers, create dialogue, and implement methods for the safe use of new therapies for FDA-approved and unlabeled indications.

Conclusion

A multidisciplinary work group developed and endorsed formal institutional prescribing and dispensing guidelines for factor VIIa (recombinant) to ensure the drug's appropriate use, minimize adverse drug events, and help contain costs. Several hospitalwide efforts were undertaken to educate medical students, residents, fellows, attending physicians, and pharmacists about the formal implementation of the evidence-based guidelines for the use of factor VIIa (recombinant).

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Appendix A—Protocols for the use of factor VIIa (recombinant)

Protocol for the use of factor VIIa (recombinant) in patients with hemophilia or warfarin toxicity^a

- I. Patients with hemophilia A or B with inhibitors (only approved indication)
 - A. High-dose factor VIII/IX is considered first-line therapy unless the patient has a history of needing factor VIIa (recombinant).
 - B. Concurrent or recent (within the past two weeks) myocardial infarction, severe angina, and stroke are strong relative contraindications to factor VIIa (recombinant). However, for patients with hemophilia with inhibitors, factor VIIa (recombinant) may be the only option.
 - C. Dosing guidelines for bleeding:
 1. Minor bleeding: 90 µg/kg i.v. for one or two doses.

2. Moderate bleeding: 90–120 µg/kg i.v. every 4 hours, then adjust to every 6 or 12 hours for one or two doses until hemostasis is achieved.
 3. Severe bleeding: 120 µg/kg i.v. every 2 hours, then adjust to every 4 or 6 hours until hemostasis is achieved. Patient may need at least 3–7 days of treatment.
- II. Reversal of warfarin toxicity in patients with serious bleeding complication (not an approved indication)
- A. Candidates for factor VIIa (recombinant) therapy:
1. Patient with an International Normalized Ratio (INR) of >2.0 who has a life-threatening bleeding episode (if benefit of receiving the drug outweighs the risk).
 2. Patient with an INR of 1.5–2.0 who has a life-threatening bleeding episode should be treated with fresh frozen plasma or vitamin K, if possible (may consider factor VIIa [recombinant] if these options do not work).
 3. Patient with an INR of <1.5 should not be treated with factor VIIa (recombinant).
 4. May consider the use of factor VIIa (recombinant) in patients receiving warfarin who are not bleeding but require an emergency procedure that cannot be delayed for 24 hours. This should be done on a case-by-case basis.
 5. Patients with a fibrinogen level of >120 mg/dL. For patients with lower fibrinogen levels, give cryoprecipitate and reassess.
 6. Strong contraindications: concurrent or recent (past two to four weeks) myocardial infarction, severe angina, or stroke. May consider using factor VIIa (recombinant) as a last resort in such patients if they have severe bleeding. However, the treating physicians, patient, and family members should all be involved in making that decision, given the risk of fatal stroke or myocardial infarction.
 7. Relative contraindications: active deep venous thromboembolism or other ongoing thrombotic event, including disseminated intravascular coagulopathy if bleeding, which is life threatening.
- B. Dosing guidelines: There is no standard dose
1. Vial sizes available: 1.2, 2.4, and 4.8 mg. Always round dose to closest full vial. Dosing must be reassessed and changes made per guidelines below as needed.
 2. INR > 5.0: 40 µg/kg i.v.; use lower dose (20–30 µg/kg) if bleeding is less severe and patient has good liver function and nutritional status allowing for vitamin K reversal.
 3. INR 3.1–5.0: 20 µg/kg i.v.; use lower dose (10 µg/kg) if bleeding is less severe and patient has good liver function and nutritional status allowing for vitamin K reversal.
 4. INR 1.5–3.0: 5–10 µg/kg i.v., depending on severity of bleeding and patient's clinical condition (i.e., how likely it is that he or she would respond quickly to vitamin K).
- C. Treatment strategy
1. Obtain stat baseline prothrombin time (PT), partial thromboplastin time, complete blood count (platelet count), and fibrinogen values.
 2. Stop warfarin.
 3. Give vitamin K to all patients. This will help limit the time during which the INR will be prolonged.
 - a. 10 mg p.o. or 5 mg i.v. if serious bleeding. Avoid s.c. and i.m. injections as they are poorly absorbed. Repeat 10 mg p.o. at 12 hours or 5 mg i.v. at 6 hours for 2–3 total doses.
 - b. 5 mg p.o. or 2 mg i.v. if bleeding is not severe and if you want to restart warfarin soon. Repeat dose at 12–24 hours until desired effect.
 4. Give factor VIIa (recombinant) (dose as above).
 5. May obtain repeat measurements of PT and INR after you have administered factor VIIa (recombinant), but it is not necessary to do so before 6 hours.
 6. Repeat INR measurements every 6 hours until bleeding stops or the INR value normalizes with vitamin K (vitamin K will take 12–36 hours to work).
 7. For surgical procedures, do not administer a test dose. Surgeon should be prepared to commence procedure after dose is given. Test dose is cost prohibitive. In addition, the risk of adverse clotting events increases if multiple doses of factor VIIa (recombinant) are given before the procedure is done (especially in patients with arterial thrombotic history).
 8. Subsequent dosing
 - a. Consider administering a second dose of factor VIIa (recombinant) at the same dose or a lower dose if patient is still bleeding at 4–6 hours or the INR is still over 2.0. Limit total doses to three.
 - b. Remember: patient is likely on warfarin because of thrombotic event or high risk of thrombosis; therefore, multiple doses of factor VIIa (recombinant) are more likely to cause a recurrent thrombotic event than would replacement with vitamin K or fresh frozen plasma.
- Protocol for the use of factor VIIa (recombinant) in patients with liver disease^a**
- I. Reversal of variceal or postprocedure bleeding in liver disease patients (not an FDA-approved indication)
- A. General considerations prior to factor VIIa (recombinant)
1. Pretreatment fibrinogen is ≥ 120 (may need cryoprecipitate or fresh frozen plasma [FFP]). Prefer to also have disseminated intravascular coagulopathy (DIC) panel and exclude hyperfibrinolysis (suspect with persistent oozing from minor puncture wounds).
 2. Consider alternatives for hyperfibrinolysis (aminocaproic acid) or uremic bleeding (desmopressin acetate).
- B. Specific situations to consider administration of factor VIIa (recombinant)
1. Active variceal bleeding uncontrolled with standard pharmacologic and endoscopic tests.
 2. Active postprocedure bleeding not controlled with more conventional therapy (catheter placement, paracentesis, thoracentesis, liver biopsy, operative wounds).
 3. Prophylactic therapy for intracranial pressure (ICP) monitor placement in fulminant hepatic failure (FHF) and thoracentesis in high-risk patients.
 - a. Consider alternative such as desmopressin acetate or use of hemodialysis in renal failure.
 - b. Target of therapy will vary depending on consultants with ICP placement. No validated guidelines for INR exist and the acceptable cutoffs vary between consultants.
- C. Precautions to administering factor VIIa (recombinant)
1. Factor VIIa (recombinant) is relatively contraindicated when the patient is on multiple pressors for hypotension (myocardial infarction risk).
 2. DIC presents a concern, though the medical literature suggests that this is more theoretical than real. Hyperfibrinolysis is unlikely to be helped by recombinant factor VIIa, so its use is not cost-efficient.
 3. Factor VIIa (recombinant) is contraindicated in patients with angina, stroke, and deep vein thrombosis (including paroxysmal ventricular tachycardia and supraventricular tachycardia). Its use

may be considered if the bleeding is active and ongoing and presents a greater immediate hazard than the risk of aggravating thrombotic disease.

D. Dose

1. The typical dose is 40 µg/kg rounded to the nearest vial size. Repeat dose is acceptable but not more than 1–2 times. Duration of effect is about 2 hours, but procedures should commence as soon after the dose as possible.
2. A lower dose (20 µg/kg) may be effective if the evidence for coagulopathy is not strong.
3. STAT ordering of postdose prothrombin time and INR may be needed (obtain 15 minutes after dose).

Protocol for the use of factor VIIa (recombinant) in patients with intracerebral hemorrhage (ICH)^a

- I. Patients with ICH (not an FDA-approved indication)
 - A. A Phase II clinical trial showed efficacy in a highly select group of patients but also suggested the possibility of an increased rate of acute myocardial infarction and ischemic stroke.⁹ The doses studied included 40, 80, and 160 µg/kg, without demonstration of a clear difference among these doses. Patients receiving anticoagulant therapy were

excluded from this trial, and the utility of factor VIIa (recombinant) in patients with ICH is not yet established.

B. ICH candidates to consider for factor VIIa (recombinant) therapy

1. Supratentorial or cerebellar ICH with rapid clinical progression, despite control of hypertension, suggesting continued hemorrhage
2. Pontine ICH
3. ICH with INR > 2.0 (vitamin K and FFP should also be given)
4. ICH or intraventricular hemorrhage with INR ≥ 1.5 requiring emergent ventriculostomy or emergent surgery (vitamin K and FFP should also be given)

C. Not necessary to measure INR before proceeding with an invasive procedure; the procedure should commence immediately after drug is administered.

D. Patients suffering ICH while receiving heparin who still have prolonged partial thromboplastin times (PTTs) when the hemorrhage is diagnosed should receive protamine to correct their PTTs.

E. Dosing guidelines: The dose of factor VIIa (recombinant) for ICH remains under study.

1. The lowest dose used in the Mayer et al.⁹ study was 40 µg/kg, but lower doses may be effective.
2. Adverse effect risks may be dose related, but this has not been established.

3. The dose should be rounded up to the closest vial size (1.2, 2.4, and 4.8 mg).

Patient Weight (kg)	Calculated dose (mg)	Closest Vial Size (mg)
50	2.0	2.4
60	2.4	2.4
70	2.8	4.8
80	3.2	4.8
90	3.6	4.8
100	4.0	4.8
110	4.4	4.8
120	4.8	4.8

4. Only a single dose should be administered.
5. Discontinue warfarin in those patients receiving warfarin and be certain that appropriate vitamin K and FFP have been administered.

Protocol for the use of factor VIIa (recombinant) in pediatrics^a

- I. Pediatrics will follow adult guidelines for respective indication.

^aThe physicians and pharmacists within the institution developed these guidelines using evidence-based practice and evidence-based medicine. These guidelines should not be used to reflect any national or formalized sanctioned guidelines.