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NovoSeven[®]: Cleveland Clinic Guidelines by Pam Risko, Pharm.D.

Introduction: Recombinant human activated Factor VII (rFVIIa), or NovoSeven[®], is a hemostatic agent which is structurally similar to human plasma-derived coagulation Factor VIIa.¹ Recombinant FVIIa is currently licensed by the US Food and Drug Administration (FDA) in patients with hemophilia A or B with inhibitors to Factor VIII or Factor IX or in patients with congenital Factor VII deficiency for the prevention of bleeding in surgical interventions or for the treatment of bleeding episodes.¹ Recommended dosing for these approved indications is provided in Table 1.

way of the coagulation cascade (Figure 1). Recombinant FVIIa triggers local coagulation at the site of vascular injury by binding to exposed tissue factor (TF).² The TF/rFVIIa complex activates clotting Factors IX and X. Activated Factor X converts prothrombin to thrombin. Thrombin can also be generated on the surface of activated platelets through activation of Factor X by rFVIIa, independent of TF.² Thrombin converts fibrinogen to fibrin, which polymerizes and forms a clot in conjunction with platelets at the site of vascular injury.

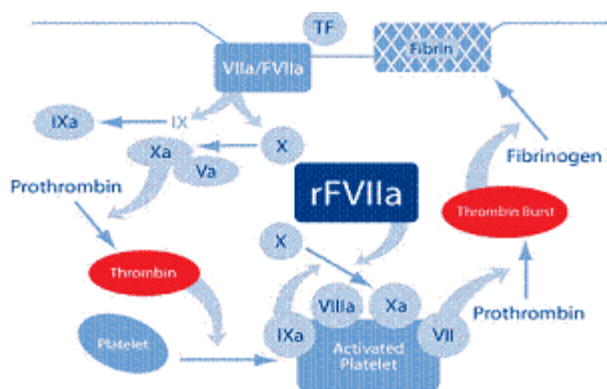
Recombinant FVIIa initiates hemostasis through activation of the extrinsic path-

In clinical studies of patients with hemophilia A or B with inhibitors, rFVIIa has been generally well toler-

Table 1. Recommended Dosing for FDA-Approved Indications of rFVIIa¹

Indication	Recommended Dose
Hemophilia A or B <ul style="list-style-type: none"> • Prevention of bleeding in surgical interventions • Treatment of bleeding episodes 	<ul style="list-style-type: none"> • 90 mcg/kg IV bolus over 2-5 minutes given immediately before intervention and repeated at 2-hour intervals for the duration of surgery • 90 mcg/kg IV bolus over 2-5 minutes every 2 hours until hemostasis is achieved or until treatment has been judged to be inadequate
Congenital Factor VII Deficiency <ul style="list-style-type: none"> • Prevention of bleeding in surgical interventions • Treatment of bleeding episodes 	<ul style="list-style-type: none"> • 15-30 mcg/kg IV bolus over 2-5 minutes every 4-6 hours until hemostasis is achieved

Figure 1. Mechanism of Action of rFVIIa



Adapted from www.novoseven-us.com

ated.¹ Adverse events that have been reported in $\geq 2\%$ of patients include: fever, hemorrhage, decreased fibrinogen, hemarthrosis, and hypertension.¹ Other possible adverse events occurring at a rate of 1% or less include: allergic reaction, arthrosis, bradycardia, coagulation disorder, disseminated intravascular coagulation (DIC), edema, increased fibrinolysis, headache, hypotension, injection site reaction, pain, pneumonia, decreased prothrombin, pruritis, purpura, rash, abnormal renal function, and vomiting.¹ However, the most serious adverse event associated with rFVIIa is thrombosis. The extent of the risk of thrombotic adverse events after treatment with rFVIIa is unknown, although it is considered to be low. Prescribing information contains a warning that patients with DIC, advanced atherosclerotic disease, crush injury, or septicemia may have an increased risk of developing thrombosis due to circulating tissue factor or predisposing coagulopathy.¹

In January 2006, a study was published reviewing all serious thromboembolic adverse events associated with rFVIIa administration which were reported to the FDA's Adverse Event Reporting System (AERS) between March 1999 and December 2004.² The AERS database contains all US and non-US mandatory and voluntary reports from both approved and off-label uses in addition to reports from patients enrolled in post-licensure clinical trials. A total of 431 reports were found, describing 185 thromboembolic events. Fifty of those events resulted in death. Off-label indications accounted for 151 (85%) of these reports. However, the authors stated that analysis of the relationship between adverse events and rFVIIa administration was hindered by the use of concomitant hemostatic medications, preexisting medical conditions, and inherent limitations of passive surveillance. The warning in the revised package insert (October 2005) includes information about thromboembolic events in patients without hemophilia.

Because rFVIIa produces local coagulation, it is an attractive agent for a variety of off-label indications including: anticoagulant therapy reversal, hepatic disease, surgical blood loss, other coagulation disorders, acute intracerebral hemorrhage,

post-traumatic hemorrhage, and thrombocytopenia. Medical literature describing the use of rFVIIa for these off-label indications is expanding rapidly. Because of the high cost of rFVIIa, many institutions have guidelines specifying indications for its off-label use. At the Cleveland Clinic, rFVIIa is currently restricted to the Departments of Hematology/Medical Oncology, Vascular Medicine, Neurology/Neurosurgery, Liver Transplant, and Cardiothoracic Surgery/Anesthesiology. Approved off-label indications at the Cleveland Clinic include: acute intracerebral hemorrhage (ICH), emergent neurosurgical intervention, fulminant hepatic failure (FHF), liver transplantation, and cardiac surgery (*all with specific patient criteria*).

Intracerebral Hemorrhage: ICH results from a spontaneous rupture of a small artery deep within the brain. It is the deadliest and most disabling form of stroke, with an estimated 30-day mortality rate of 30-50%.⁴ Current medical management is mainly supportive and consists of blood pressure control, intracranial pressure monitoring, fluid administration, body temperature control, and prevention of seizures.⁴ Surgical interventions have not shown to improve outcomes. However, it is well recognized that early hematoma growth occurs in 18-38% of patients receiving CT scans within 3 hours of ICH onset and is associated with poor outcomes.⁵ Therefore, the administration of rFVIIa to promote hemostasis may improve outcomes.

A Phase II dose-ranging trial was conducted by Mayer and colleagues between August 2002 and March 2004 to determine whether rFVIIa effectively reduces hematoma growth after ICH.⁵ Three hundred ninety-nine patients with acute ICH diagnosed by CT scan within 3 hours after onset were randomized to receive a single dose of either 40-, 80-, or 160-mcg/kg of rFVIIa or placebo within 1 hour after the baseline scan. The primary outcome was the percent change in hematoma volume at 24 hours. Clinical outcomes were assessed at 90 days. The mean increase in hematoma volume was 29% in the placebo group as compared with 14% in the rFVIIa groups ($p=0.01$). A dose-response effect was evident for the reduction of hemorrhage growth. The small-

est effect occurred with the rFVIIa 40 mcg/kg dose, while the most substantial effect occurred with the 160 mcg/kg dose. Mortality at 90 days was 29% in the placebo group versus 18% in the three rFVIIa groups combined ($p=0.02$). Serious thromboembolic adverse events occurred in 7% of patients treated with rFVIIa versus 2% of patients administered placebo ($p=0.12$). The authors concluded that treatment of ICH with rFVIIa within 4 hours after onset of symptoms limited the growth of hematoma, reduced mortality, and improved functional outcomes at 90 days, despite a small increase in the frequency of serious adverse events.

The Factor Seven for Acute Hemorrhagic Stroke Treatment (FAST) trial is a Phase III trial ($n=675$) to confirm the beneficial effect of rFVIIa.⁴ Patients were randomized to receive rFVIIa 20 mcg/kg, 80 mcg/kg, or placebo. Results from this trial are not yet published, but are available in abstract form.^{5a}

Guidelines for the use of rFVIIa in ICH were implemented at the Cleveland Clinic in May 2006. Dosing recommendations are provided in Table 2.

Emergent Neurosurgical Intervention: Emergent coagulopathy reversal is often needed in patients necessitating neurosurgical interventions such as a craniotomy or placement of an intracranial bolt or ventricular catheter.⁴ It is generally accepted by convention that most neurosurgeons require a documented International Normalized Ratio (INR) value below 1.4 before proceeding with the intervention.⁴ There are several case reports and case series demonstrating the beneficial effect of rFVIIa for rapid correction of warfarin-induced coagulopathy before neurosurgical interventions. Recombinant FVIIa has been used successfully in the management of coagulopathic patients with intracranial parenchymal hemorrhage, subdural or epidural hematoma, subarachnoid hemorrhage, and hydrocephalus requiring an intraventricular catheter.

In the largest retrospective review to date, 29 patients were administered rFVIIa as second-line therapy after initial attempts at reversal of coagulopathy with fresh frozen plasma (FFP) were unsuccessful.⁶ The control group was composed of 24 patients treated with FFP and vitamin K alone. In the rFVIIa group, the INR was significantly reduced from 2.2 to 1.1 ($p<0.05$) after an average dose of 1.4 mg of rFVIIa. The INR in the rFVIIa group normalized in 6.78 ± 2.68 hours after admission versus 47.44 ± 9.88 hours in the control group ($p<0.0005$). No thrombotic complications were observed in patients administered rFVIIa.

Guidelines for the use of rFVIIa in coagulopathic patients requiring emergent neurosurgical interventions were approved at the Cleveland Clinic in May 2006. Dosing recommendations are provided in Table 2.

Fulminant Hepatic Failure: Patients with FHF develop complex coagulopathies, predominantly decreased produc-

tion of coagulation factors. During liver transplantation, the coagulopathy often worsens due to dilution of coagulation factors and platelets and activation of fibrinolysis. Recombinant FVIIa was first reported to be used in liver transplantation in 1999.⁷ In this setting, rFVIIa has appeared to be promising in both FHF patients undergoing placement of intracranial pressure (ICP) monitors and intra-operatively as rescue therapy in patients undergoing transplantation.⁷

Severe coagulopathy in FHF increases the risk for procedure-related bleeding. A common invasive procedure in this patient population includes the placement of an ICP transducer in order to monitor ICP perioperatively.⁸ Conventional treatment with FFP often is unsuccessful and may require large administration volumes, leading to volume overload and anasarca. Factor VII is the first coagulation factor to have decreased levels in patients with FHF.⁸ Therefore, it is reasonable to believe that the administration of rFVIIa should promote hemostasis in FHF.

Several case reports, case series, and small retrospective case cohort reviews have evaluated the use of rFVIIa to improve coagulation in FHF. In the largest retrospective review to date, 15 patients with FHF who met criteria for liver transplantation were studied.⁸ Eight consecutive patients were administered FFP alone and 7 consecutive patients were administered FFP and rFVIIa (40 mcg/kg IV bolus) for correction of coagulopathy to facilitate placement of ICP monitors. All patients administered rFVIIa versus no patients administered FFP alone had a temporary (2-6 hours) correction of coagulopathy. All patients administered rFVIIa versus 38% of patients administered FFP alone were able to have an ICP transducer placed. Bleeding complications developed in two patients administered FFP alone compared with none of the patients administered rFVIIa. There were no thrombotic complications observed in patients administered rFVIIa. The authors concluded that rFVIIa is effective in transiently correcting laboratory parameters of coagulopathy in patients with FHF.

In January 2007 Cleveland Clinic approved recombinant FVIIa use for patients with FHF to permit insertion of an ICP monitor in patients with coagulopathy who are either unresponsive to conventional measures or unable to tolerate the large volume load of FFP. Guidelines for administration are provided in Table 2.

Liver Transplantation: In some patients undergoing liver transplantation, excessive bleeding persists despite exhaustive surgical control attempts and conventional therapy to control coagulopathy.⁹ In most situations, blood products and antifibrinolytic agents can correct the coagulopathy. However, if the coagulopathy continues or worsens and the patient becomes unstable, alternative strategies such as rFVIIa should be considered.⁹ Currently, there is no universally accepted definition of "failed maximal conventional therapy." In addition, it is unlikely that a randomized placebo-controlled trial will ever be conducted to evaluate the

use of rFVIIa as rescue therapy. Therefore, the decision to use rFVIIa in this setting is best determined using a multidisciplinary approach considering the risks versus benefits of therapy. It is recommended that each institution develop a protocol for rFVIIa administration with guidelines for dosing and appropriate follow-up.⁹

In January 2007 recombinant FVIIa was approved for use at the Cleveland Clinic for rescue therapy during liver transplantation in patients with life-threatening bleeding and severe coagulopathy unresponsive to conventional measures and surgical control attempts. Guidelines for administration are provided in Table 2.

Cardiothoracic Surgery: Post-operative bleeding is a common complication following cardiothoracic surgical procedures and is associated with increased healthcare costs, morbidity, and mortality.¹⁰ Bleeding may result from impaired platelet function due to pre-operative medication and cardiopulmonary bypass,

consumption of platelets, dilution of coagulation proteins, and triggering of fibrinolysis.¹¹ Treatment strategies include supportive care with volume resuscitation, the administration of blood products, pharmacologic intervention with hemostatic agents, and surgical reexploration. Blood products have a relatively high rate of transfusion-related reactions and adverse effects as well as the potential for disease transmission. Pharmacologic agents such as protamine, aprotinin (Trasylol[®]; restricted at Cleveland Clinic), aminocaproic acid (Amicar[®]), tranexamic acid (Cyklokapron[®]), and desmopressin (DDAVP[®]) have been used; however, many patients with severe post-operative bleeding are unresponsive to these drugs. Massive hemorrhage requiring surgical reexploration occurs in about 6% of patients and is associated with considerable morbidity and mortality.

Recombinant rFVIIa has been used as rescue therapy for major coagulopathic bleeding in cardiac surgery. In addition, it has also been occasionally used as prophylaxis for

Table 2. Approved Cleveland Clinic Guidelines for rFVIIa Dosing*

Indication	Recommended Dose	Comments
Intracranial hemorrhage	<ul style="list-style-type: none"> 80 mcg/kg IV push over 2-5 minutes x 1 dose 	<ul style="list-style-type: none"> Onset of symptoms to time of presentation < 3 hours GCS > 5 off sedation and neuromuscular blockers
Emergent neurosurgical intervention	<ul style="list-style-type: none"> 80 mcg/kg IV push over 2-5 minutes x 1 dose 	<ul style="list-style-type: none"> INR ≥ 1.4 Additional administration of corrective therapies such as FFP, platelets, and cryoprecipitate considered mandatory in absence of contraindications
Fulminant hepatic failure	<ul style="list-style-type: none"> 80 mcg/kg IV push over 2-5 minutes x 1 dose 	<ul style="list-style-type: none"> To permit insertion of ICP monitor in patients with coagulopathy Either unresponsive to conventional measures or unable to tolerate volume load of FFP
Liver transplantation	<ul style="list-style-type: none"> 80 mcg/kg IV push over 2-5 minutes x 1 dose May repeat 80 mcg/kg dose once in 2 hours if bleeding continues 	<ul style="list-style-type: none"> Rescue treatment intra-operatively in patients with life-threatening bleeding and severe coagulopathy Unresponsive to conventional measures and surgical control attempts
Cardiac surgery - prophylaxis	<ul style="list-style-type: none"> 90 mcg/kg IV push over 2-5 minutes x 1 dose May repeat 90 mcg/kg dose once in 2-3 hours if bleeding continues 	<ul style="list-style-type: none"> Critically ill patients with a known history of coagulopathy or active bleeding
Cardiac surgery	<ul style="list-style-type: none"> 90 mcg/kg IV push over 2-5 minutes x 1 dose May repeat 90 mcg/kg dose once in 2 hours if bleeding continues 	<ul style="list-style-type: none"> Continued bleeding despite aggressive correction with blood and blood products Labs confirming a coagulopathy should be obtained if possible

**Dosing should be based on actual body weight (ABW). If the patient is obese (≥25% over Ideal Body Weight [IBW]), then the dose should be based on an adjusted body weight (AdjBW = IBW + 0.4[ABW-IBW]). Additionally, to decrease waste of any unused portion of a vial, the dose should be rounded to the nearest 1.2 mg. The smallest vial size available is 1.2 mg.*

bleeding in complex cardiac surgery. The majority of the literature supporting rFVIIa for cardiac surgery consists of case reports and case series.

A randomized, double-blind, placebo-controlled pilot study of 20 patients undergoing complex non-coronary cardiac surgery was conducted to evaluate if rFVIIa reduced the need for allogeneic blood transfusion.¹² Patients were randomized to receive either rFVIIa 90 mcg/kg IV bolus or placebo after cardiopulmonary bypass and reversal of heparin. Two patients in the rFVIIa group received a total of 13 units of blood products compared to 8 patients in the placebo group receiving a total of 105 units of blood products. All patients in this study received aprotinin. There were no differences between the groups in length of ICU or hospital stay, ventilation time, or the development of adverse thrombotic events. The authors concluded that despite study limitations, rFVIIa significantly reduced the need for allogeneic transfusion in complex non-coronary cardiac surgery without causing adverse events.

Most recently, rFVIIa was approved at the Cleveland Clinic in April 2007 for use as prophylaxis in high-risk patients undergoing elective cardiac surgery and for the treatment of excessive blood loss in cardiac surgery after which all other therapeutic measures have failed. Guidelines for administration are provided in Table 2.

Cost Information: The average wholesale price (AWP) of NovoSeven[®] is \$1.58 per microgram (mcg).¹³ For a 70 kg patient, the drug cost of an 80 mcg/kg dose is \$9,480 (80 mcg/kg/dose x 70 kg = 5,600 mcg; then, the dose is rounded to the nearest 1.2 mg to decrease waste = 6,000 mcg x \$1.58 = \$9,480).

Conclusion: Recombinant human activated Factor VII is FDA-approved for hemophilia A and B and for congenital Factor VII deficiency. Recently, it is being used for a variety of off-label indications. Based on published literature and expert opinion, the Cleveland Clinic Pharmacy and Therapeutics Committee approved the use of rVIIa for select off-label indications when patients meet certain criteria. These criteria are to optimize the efficacy of rVIIa and to minimize the adverse effects and cost of rFVIIa. The Cleveland Clinic Pharmacy and Therapeutics Committee will continue to evaluate these off-label indications and any new pertinent data for rFVIIa altering criteria or indications if appropriate.

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**Cleveland Clinic
Pharmacy and Therapeutics Committee
Automatic Therapeutic Interchange
Levalbuterol to Albuterol
September 2007**

On Tuesday, September 25, 2007, all **new** medication orders for adult and pediatric inpatients for initiation of levalbuterol (Xopenex[®] nebulizer and metered dose inhalers) will be automatically converted to albuterol by the pharmacist.

A new pre-printed Respiratory Therapy Medication Order Form will be used. The new pre-printed order form does NOT include levalbuterol, and levalbuterol may NOT be written in the "Other" section on the form.

If a patient has been on levalbuterol at home and a prescriber wants the patient to continue to receive levalbuterol during the inpatient admission, the prescriber must write the levalbuterol order on a separate Physician Order Sheet (i.e., not on the pre-printed Respiratory Therapy form) and state **continuation of therapy from home** (i.e., patient is already on levalbuterol at home prior to admission). In Epic, the pharmacist should verify that the patient has been on levalbuterol at home. If this information is not in Epic and continuation of therapy from home is not stated on the order, then the pharmacist needs to contact the prescriber to confirm.

Dose Conversion for Levalbuterol to Albuterol:

Nebulizer

Adults and Pediatric Patients:

Levalbuterol 0.63 mg or 1.25 mg inhalation any frequency = Albuterol (0.083%) 2.5 mg inhalation Q 4 hr

Metered-Dose Inhaler (MDI)

Adults and Pediatric Patients:

Levalbuterol HFA (45 mcg per actuation) inhale 1-2 puffs Q 4-6 hr =
Albuterol HFA (90 mcg per actuation) inhale 1-2 puffs Q 4 hr

If the levalbuterol order is for a scheduled frequency (Q 4 hr or Q 6 hr or Q 8 hr), then the albuterol conversion would be for a scheduled frequency (Q 4 hr). If the levalbuterol order is for a PRN frequency (Q 4 hr PRN or Q 6 hr PRN, or Q 8hr PRN), then the albuterol conversion would be for a PRN frequency (Q 4 hr PRN).

If the patient is still symptomatic with albuterol 2.5 mg Q 4 hr, then a prn order for albuterol may be written or the frequency may be increased on the albuterol order by the physician.

Background: Albuterol is a racemic mixture of (R)-albuterol and (S)-albuterol. Levalbuterol (Xopenex[®]) is the single enantiomer of albuterol, specifically (R)-albuterol. The bronchodilating activity of albuterol is due to the (R)-isomer and some of the side effects may be due to the (S)-isomer. However, no *consistent* clinical difference in bronchodilation, bronchoprotection, or side effects (e.g., tachycardia) has been documented between albuterol and levalbuterol.

The CC Pharmacy and Therapeutics Committee in conjunction with the Medical Directors of the Respiratory Therapy Departments approved the interchange from levalbuterol to albuterol for initiation of therapy, and there are specific directions for the continuation of levalbuterol therapy from home. If you have any questions, contact the Drug Information Center (216-444-6456, option 1).

Cleveland Clinic
Pharmacy and Therapeutics Committee
Automatic Therapeutic Interchange
Promethazine injection to Ondansetron injection
October 2007

On **October 30, 2007** injectable promethazine (Phenergan[®]) will be removed from the Cleveland Clinic Formulary. All **new** orders written for injectable (IV/IM) promethazine **outside of a designated PACU** (PACU areas are E20, H20, M20, M21, M22, and M23) will be automatically converted to ondansetron (generic Zofran[®]) IV by the pharmacists.

All **new** orders written for injectable promethazine **when a patient is in a PACU** (PACU areas are E20, H20, M20, M21, M22, and M23), the pharmacist must contact the prescriber to discuss an alternative antiemetic. The reason is that if the patient received ondansetron in the operating room (OR) for prevention of post-operative nausea and vomiting (PONV), then administration of ondansetron in the PACU for the treatment of PONV (“rescue”) most likely will not be effective. Therefore, the pharmacist should discuss with the prescriber other antiemetic rescue medications for PACU patients.

Medication orders for oral and rectal promethazine will not be interchanged (i.e., this interchange only affects IV/IM promethazine).

Dose Conversion for Promethazine IV/IM to Ondansetron IV

Promethazine 6.25 to 50 mg IV or IM any frequency scheduled =
Ondansetron 4 mg IV Q 6 hrs

Promethazine 6.25 to 50 mg IV or IM any frequency PRN =
Ondansetron 4 mg IV Q 6 hrs PRN

If the prescriber does not want ondansetron to be administered to the patient as a therapeutic substitution for promethazine, please contact the Drug Information Center (216-444-6456, option 1) for antiemetic alternatives.

Background: Promethazine injection is a commonly used product that possesses antihistamine, sedative, anti-motion sickness, and antiemetic effects. The drug is also a known vesicant which is highly caustic to the intima of blood vessels and surrounding tissue. Formulated with phenol, promethazine has a pH between 4 and 5.5. Although deep intramuscular injection into a large muscle is the preferred parenteral route of administration, product labeling states that the drug may be given by slow intravenous (IV) push. However, due to the frequency of severe, tragic, local injuries after infiltration or inadvertent intra-arterial injection, the Institute for Safe Medication Practices (ISMP) has recommended that the FDA reexamine the product labeling and consider eliminating the IV route of administration.

Severe tissue damage can occur regardless of the route of parenteral administration, although intravenous and inadvertent intra-arterial or subcutaneous administration results in more significant complications, including: burning, erythema, pain, swelling, severe spasm of vessels, thrombophlebitis, venous thrombosis, phlebitis, nerve damage, paralysis, abscess, tissue necrosis, and gangrene. Sometimes surgical intervention has been required, including fasciotomy, skin graft, and even amputation.

The true extent of this problem may be unknown. However, scores of reports submitted to ISMP, United States Pharmacopeia, the Pennsylvania Patient Safety Reporting System; articles in professional literature; and news of lawsuits in the media suggest that patient harm may be occurring more frequently than recognized. Source: ISMP website available at: <http://www.ismp.org/Newsletters/acutecare/articles/20060810.aspte> (accessed Sunday July 15, 2007)

As a result of the recommendations from ISMP, the Cleveland Clinic Pharmacy and Therapeutics Committee approved the removal of IV/IM promethazine from formulary. Any orders written for IV/IM promethazine will be automatically converted to IV ondansetron. Notification of the interchange will be written for each patient by pharmacy and placed in the patient's chart. If you have any questions, please contact the Drug Information Center (216-444-6456, option 1).