RECOMMENDATIONS CONCERNING (NONFORMULARY) OFF-LABEL USE OF RECOMBINANT ACTIVATED HUMAN COAGULATION FACTOR SEVEN (rFVIIa) (NOVOSEVEN®)

VHA Pharmacy Benefits Management Strategic Healthcare Group And the Medical Advisory Panel

The following recommendations are based on current medical evidence. The content of the document is dynamic and will be revised as new clinical data become available. The purpose of this document is to assist practitioners in clinical decision making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

Novoseven® is a recombinant preparation of activated human coagulation factor VII (rFVIIa). The Food and Drug Administration (FDA) approved rFVIIa in March of 1999 for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to Factor VIII or IX and in those with congenital Factor VII deficiency. It is also approved for the prevention of bleeding prior to surgical interventions or invasive procedures in similar patients.

Over the past several years, there has been increasing interest in using rFVIIa for off-label indications. This interest is demonstrated by the large amount of published data examining the many off-label uses of rFVIIa. However, the bulk of the evidence is in the form of case reports and case series with no control group making it very difficult to determine actual benefit and safety in treating various conditions. In addition, with case reports and case series making up the bulk of the evidence, there is a potential for bias of various types including selection of patients, varied doses and dosing regimens, and finally submitting only positive data for publication. Because there are only a limited number of published controlled trials prospectively evaluating rFVIIa for these various off-label conditions, the appropriate dose for each indication, the dosing interval, whether or not to combine rFVIIa with other hemostatic agents (e.g. antifibrinolytics-aminocaproic acid or tranxemic acid or aPCCs or PCCs), optimal timing for use, need for repeat doses, etc. is not clear. There are numerous clinical trials underway in a variety of conditions. For more information, go to http://www.clinicaltrials.gov/ct and type Novoseven® in the search box.

In December 2005, the FDA and Novo Nordisk alerted healthcare professionals of several labeling changes concerning the safety of recombinant coagulation factor VIIa or rFVIIa (Novoseven®) in non-hemophiliac patients. These changes are reflected in the warnings and adverse reactions sections of the label and originate from data from clinical trials in non-hemophiliac patients and from post marketing surveillance. Essentially, the labeling states that the risk for thromboembolism in patients with hemophilia is unknown but is thought to be low. However, the new labeling warns of a potentially increased thromboembolic risk in nonhemophiliac patients especially in those with circulating tissue factor or predisposing coagulopathy (e.g. disseminated intravascular coagulation {DIC}, advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with activated or nonactivated prothrombin complex concentrates {aPCCs/PCCs}).

Because of the increasing potential for the off-label prescribing of rFVIIa; the unknown efficacy and safety of rFVIIa in managing various off-label indications; and rFVIIa's high acquisition cost, VA MedSafe and the Medical Advisory Panel (MAP) conducted a review of the published controlled clinical trials and provided recommendations for use (Link). Please refer to this link for more detailed information supporting the recommendations, below. These recommendations are for use by local Pharmacy & Therapeutics (P&T) Committees, as well as by individual providers, in determining how and when this agent may be utilized.

Recombinant FVIIa was developed as a bypassing agent intended for use in those patients with inhibitors to coagulation factors VIII or IX. However, many off-label uses of rFVIIa do not involve patients with inhibiting antibodies. As a result, standard therapeutic measures for bleeding cessation (e.g. vitamin K, transfusion of FFP, cryoprecipitate, RBC or platelets, prothrombin complex concentrates, topical hemostatics, etc.) should be exhausted or proven ineffective prior to consideration of rFVIIa. (This agent should only be used in cases where cessation of bleeding is expected to alter overall prognosis and/or survival).

RECOMMEND FOR CONSIDERATION (Quality of Evidence/Strength of Recommendation)

rFVIIa may be considered in the following situations:

- **Intracerebral hemorrhage** (1B-one study) **IF**: (All criteria must be met)
  a. Symptom onset <4 hrs
  b. Glasgow Coma Scale >5
  c. No plan for surgical evacuation within 24 hrs
  d. No history of thrombotic or vaso-occlusive disease (nonstatistical increase in serious thromboembolic events in the rFVIIa group vs. placebo 7% vs. 2%, respectively)

RECOMMEND AGAINST USE (Quality of Evidence/Strength of Recommendation)
(Because of a lack of data and/or data demonstrating ineffectiveness or harm)

rFVIIa should NOT be utilized in the following situations: (Because of lack of benefit or harm)

- **Cessation of variceal bleeding/prevention of variceal rebleeding in patients with cirrhosis** (1B-one study showing no benefit in bleeding cessation, rebleeding or death at 24 hrs or 5 days)

Surgery:

- **Preoperative use (at first incision) in major liver resection** (1A-two studies showing no reduction in RBC transfused)
- **Preoperative (at first incision) and/or planned perioperative use in orthotopic liver transplantation** (1A-two studies showing no reduction in RBC transfused)
- **Preoperative use (at first incision) in patients undergoing major reconstructive surgery for pelvic or pelvic-acetabular fracture** (1B-one study showing no reduction in transfusion of blood products or number transfused)

rFVIIa use is UNCLEAR in the following situations. The lack of evidence suggests use should be considered only when standard/conventional treatments have been exhausted or proven ineffective.

- **Reversal of prolonged prothrombin time (PT) prior to invasive procedures (e.g. liver biopsy) in patients with liver disease** (3C- three case series, no control group, unknown effectiveness in bleeding after procedure)
- **Reversal of anticoagulation** (3C-No trials comparing rFVIIa with FFP and/or vitamin K for reversal of excessive anticoagulation with warfarin. As for fondaparinux, there is one study in healthy, nonbleeding volunteers. The benefit/risk ratio of rFVIIa in bleeding patients due to fondaparinux is unknown).
- **Other Hereditary Coagulation Disorders/Platelet Function Defects** (3C-unknown effectiveness, no controlled trials)
  a. Consider only after standard treatments have proven inadequate and/or patient has developed inhibitors to clotting factors.

Surgery/Trauma:

- **Retropubic prostatectomy** (1B-one small study of 36 patients. Insufficient evidence to judge benefit vs. harms so cannot recommend for routine use)
- **Intractable bleeding associated with surgery or trauma** (3C-unknown effectiveness due to the difficulty in

prospectively studying this heterogenous group in the midst of an emergent condition). **Standard/conventional treatments for bleeding cessation should be exhausted or proven ineffective prior to consideration/ utilization of this therapy.**

a. One study in blunt and penetrating trauma. Blunt trauma-reduced number of RBC transfusions (after then 8th unit) and need for massive transfusion (>20 units RBC) but no difference in 48 hr. or 30 day survival. No benefit observed in penetrating trauma.
b. Less likely to respond to rFVIIa-Patients with RTS >4.09, PT ≥ 17.9 seconds and severe acidosis (pH<7) and profound shock.
c. The American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies identify rFVIIa as an appropriate rescue drug when traditional, well-tested options have been exhausted (Anesthesiology 2006;105:198-208).

- **Severe, intractable bleeding associated with cardiac surgery.** (3C-no randomized controlled trials evaluating safety and benefit). **Standard/conventional treatments for bleeding cessation should be exhausted prior to consideration/utilization of this therapy.**
  a. There are very limited data in using rFVIIa as a rescue intervention in patients having CABG surgery. The risk for graft thrombosis is not known but may be increased. Additionally, the thromboembolic risk in these patients with atherosclerotic plaques in other coronary arteries is not known but may be increased.

Dosage and Administration

At this time, there is insufficient evidence to suggest a particular dose for off-label indications. Additionally, from the available data, there is not a clear dose-response relationship for achieving hemostasis. However, one group has recommended a 4.8 mg vial in appropriate patients providing a dose of 50-100 mcg/kg in individuals weighing 50-100 kg. While another group has recommended a dose of 20-40 mcg/kg for nonemergent anticoagulation reversal and doses of 41-90 mcg/kg for other appropriate scenarios. (See full review for citations and for doses studied –LINK HERE).

Timing of administration or need for repeat dosing is not known.

Monitoring

Laboratory coagulation parameters (e.g. PT, aPTT) may be monitored together with monitoring for clinical signs of a hemostatic response. However, there is no evidence correlating achievement of hemostasis and an effect of rFVIIa on these coagulation parameters.

Precautions/Warnings

- In the warnings section of the product labeling, it is stated that the risk for thromboembolic events in patients with hemophilia and inhibitors is unknown, but is considered to be low. However, patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs/PCCs) may have an increased risk for developing a thrombotic event due to circulating tissue factor (TF) or predisposing coagulopathy.

- Although there is a lack of evidence, some recommend avoiding rFVIIa in patients who have received or will receive aPCCs or PCCs due to the increased possibility for a thromboembolic event.

- Recombinant activated FVII is contraindicated in patients with a known hypersensitivity to mouse, bovine or hamster proteins.