COAGULATION FACTOR PRODUCTS

PRODUCT	CLASS
Helixate FS Kogenate FS Bioclate Recombinate ReFacto* Advate**	Recombinant Factor VIII
Monarc M Monoclate P Hemofile M	Human-derived Factor VIII
Benefix	Recombinant Factor IX
Alphanine SD Mononine	Human-derived Factor IX
Humate P Alphanate Koate DVI	Factor VIII with von Willebrand Factor
Feiba VH Autoplex T Bebulin VH Proplex-T Profilnine SD	Anti-Inhibitor Coagulant
NovoSeven	Recombinant Factor VIIa

*B-domain depleted product

**plasma/albumin free manufacturing

FACTOR REPLACEMENT (VIIa)

RECOMBINANT FACTOR VIIa
(NOVOSEVEN®)

I. MECHANISM OF ACTION
Recombinant Factor VIIa is a recombinant glycoprotein similar to coagulation Factor VIIa (rVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade. rVIIa is structurally similar to human plasma-derived factor VIIa and when complexed with tissue factor, can activate Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. In complex with other factors, Factor Xa converts prothrombin to thrombin. The generation of thrombin allows for the formation of a hemostatic plug through conversion of fibrinogen to fibrin thereby promoting local hemostasis both on the endothelial surface and on the platelet surface. It also exerts its effects through tissue factor independent mechanisms and has also been shown to activate platelets. rVIIa is FDA approved for treatment of hemophilia A or B patients with acquired inhibitors to factor VIII or IX. It has also been used off label in the treatment of factor VII deficiency, von Willebrand's disease, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, liver disease, intracranial hemorrhage, traumatic or operative bleeding that failed to respond to standard measures, reversal of warfarin, and other causes of life threatening bleeding.

II. PHARMACOKINETICS
A) rVIIa exhibits dose-dependent pharmacokinetics.
B) The peak factor VII activity level (FVII:C) following an initial 70 mcg/kg dose of rVIIa is 20 Units/mL and following a 35 mcg dose is 10.8 Units/mL.
C) The median clearance of rVIIa is 33 mL/kg/hour.
D) The half life of rVIIa is 2.3 hours.
E) The median *in vivo* plasma recovery is 44%.
F) The median volume of distribution at steady state is 103 mL/kg.

III. DOSAGE AND ADMINISTRATION
A) rVIIa is only available for use as an intravenous infusion.
B) Due to the short half-life of rVIIa frequent dosing is necessary.
C) For hemophilia A or B patients with inhibitors the recommended dose is 90 mcg/kg given every 2 hours until hemostasis is achieved.
D) Doses between 35-120 mcg/kg have been used successfully in clinical trials.
E) Dose and frequency should be adjusted based on therapeutic response.
F) Higher doses used at less frequent intervals have been used and continue to be studied.
G) For factor VII deficient patients and for reversal of warfarin lower doses have been used and found to be efficacious. Doses between 15-30 mcg/kg adjusted and repeated based on response is recommended.
H) Doses vary for other off label use.
I) No adjustment is thought necessary for renal or hepatic impairment.

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IV. TOXICITY

A) Generally well tolerated.
B) The extent of thrombotic events after treatment with rVIIa is elevated in certain subsets of patients, but overall appears to be low. Risk increases with higher doses and repeated dosing.
C) Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, or septicemia may have an increased thrombotic risk.
D) Pregnancy Category C.

V. CLINICAL MONITORING

A) In hemophiliac patients Factor VIII levels will not change significantly after administration of rVIIa. Efficacy should be monitored clinically and be based upon hemodynamics, levels of bleeding, and pain.
B) Administration of rVIIa reduces the prothrombin time (PT) and activated partial thromboplastin time, but should not be used to monitor efficacy in hemophilia A and B patients with inhibitors.
C) PT may be used for monitoring in Factor VII deficient patients, warfarin reversal or those with bleeding of unknown cause.
D) Factor VII activity level (FVII:C) can be measured in factor VII deficient patients.

VI. DRUG INTERACTIONS

A) The risk of a potential interaction between rVIIa and coagulation concentrates has not been adequately evaluated in preclinical or clinical trials.
B) Simultaneous use of activated prothrombin complex concentrates (aPCCs) or prothrombin complex concentrates should be avoided.
C) Although not well studied the concomitant use of antifibrinolytic therapy (tranexamic acid, aminocaproic acid) has been reported without adverse sequelae.

VII. SPECIAL

rVIIa is prohibitively expensive and its use in hemophiliac patients with inhibitors should be in conjunction with the pediatric or adult hematology consult services. Optimal dose and frequency of administration remains uncertain both in hemophilia A or B patients with inhibitors as well as in the many off label uses of this drug. Given the cost of the drug, consideration should be given to rounding the dose to vials size when clinically appropriate.

PROTOCOL FOR OFF-LABEL (NON-HEMOPHILIA) USE OF RECOMBINANT FACTOR VIIa

GENERAL COMMENTS:

All rVIIa use will be concurrently monitored for protocol refinement.

Emergent use of rVIIa in the setting of life-threatening bleed will be reviewed retrospectively for compliance with guidelines. For non-emergent use of rVIIa, the hematology service is available for consultation should questions regarding hemostasis arise.

How supplied and Cost (as of 8/13/08)
Vial sizes: 1 mg $1,050
2 mg $2,100
5 mg $5,250

Initial recommended dose: Up to 45 mcg/kg for perioperative surgery, including cardiac surgery cases; 5 mg for trauma cases.
When possible, use of rVIIa should be in conjunction with the Massive Transfusion Protocol.

ALL DOSES WILL BE ROUNDED TO NEAREST 1 mg DOSE (unless total dose is less than 1 mg).

INDICATIONS: See Tables below.

GENERAL CONTRAINDICATIONS:

A) Hypersensitivity to mouse, bovine, or hamster proteins
B) Hypersensitivity to rVIIa or product components

GENERAL EXCLUSIONS:

A) Futile care
B) Pregnancy (Exception: Patient with Factor VII deficiency at delivery in consultation with hematology)
C) Prophylaxis for potential bleeds (Exception: Patients with hemophilia and Factor VIII or IX inhibitor or with Factor VII deficiency in consultation with hematology)
D) DIC

WARNINGS/PRECAUTIONS:

Increased risk of thrombotic events
Risk factors include:
A) History of CAD
B) History of venous or arterial thrombosis
C) Crush injury
D) Disseminated intravascular coagulation (DIC)
E) Septicemia
F) ECMO or VAD
G) Post cardiac surgery
H) Cerebral vascular disease

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DRUG INTERACTIONS:

A) Avoid simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates.

ADVERSE EVENTS:

A) Thrombosis
B) Fever
C) Hypertension
D) Allergic reaction
E) DIC

MONITORING:

A) CBC, PT/INR, PTT, Fibrinogen, and ABG (for pH) are suggested prior to administration of rVIIa. Thromboelastograph (TEG) may be considered in select cases.
B) Degree of bleeding should be reassessed 20-30 minutes after initial dose for either resolution of bleeding or excessive bleeding. Re-address blood product administration, surgical exploration for source of bleeding, or consider redosing rVIIa if excessive bleeding continues.

RECOMBINANT FACTOR FVIIA (rVIIA) DOSING GUIDELINES IN THE TREATMENT OF NON-HEMOPHILIAC BLEEDINGS IN VARIOUS CLINICAL SETTINGS

INDICATIONS	RFVIIA DOSE	OTHER MEASURES	MONITORING PARAMETERS
[a] UNCONTROLLED HEMORRHAGE ASSOCIATED WITH:			
Severe liver failure with GI bleed or liver transplant (For adults, rVIIa use only restricted to cirrhotic patients with Child-Pugh grade B & C, but not grade A)	**Adults:** 100 mcg/kg IV bolus for 1 dose. If there is clinical response, may repeat up to 8 doses. (round off to 1,200 mcg increments) **Pediatrics:** 40-90 mcg/kg IV bolus for 1 dose. If there is clinical response, may repeat up to 6-8 doses. (round off to 1200 mcg increments)	Continue to replace consumed/diluted hemostatic factors with FFP, cryoprecipitate, platelet and PRBC transfusion. If pt is septic, [c]acidosis and [d]hypothermia should be corrected prior to rVIIa treatment.	PT, aPTT, fibrinogen, D-dimer, FSP, CBC, prior to and after rVIIa, check pH, body temperature if clinically indicated.
Cardiothoracic surgery	**Adults:** 3.6 mg IV for 1 dose. If there is clinical response, may repeat times one within 2 hours. **Pediatrics:** 50 mcg/kg IV bolus times one, and may repeat up to 4 doses every 1 hour as needed. (round off to 1200 mcg increments)	Continue to replace consumed/diluted hemostatic factors with FFP, cryoprecipitate, platelet and PRBC transfusion. If pt is septic, [c]acidosis and [d]hypothermia should be corrected prior to rVIIa treatment.	CBC and coagulation parameters (PT, aPTT, fibrinogen, D-dimer, FSP) prior to rVIIa dose, and 1 hour and 24 hours after administration. Check pH, body temperature if clinically indicated.
Trauma or Emergency Surgery or Burns	Follow Shands Trauma/Surgery protocol (see Appendix A): 120 mcg/kg IV bolus times one, may repeat times one more dose if needed (round off to 1200 mcg increments)	Continue to replace consumed/diluted hemostatic factors with FFP, cryoprecipitate, platelet and PRBC transfusion. If pt is septic, [d]acidosis and [e]hypothermia should be corrected prior to rVIIa treatment.	PT, aPTT, fibrinogen, D-dimer, FSP, CBC, prior to & after rVIIa, Check pH, body temperature if clinically indicated.
ACUTE INTRACRANIAL HEMORRHAGE WITH OR WITHOUT COAGULATION PARAMETERS			
Acute intracranial hemorrhage within 3 hours of onset of symptoms	Dose: 80 mcg/kg IV bolus times one dose only. (round off to 1200 mcg increments)		PT, aPTT, fibrinogen, D-dimer, FSP, CBC, prior to and after rVIIa
RAPID ANTICOAGULANT REVERSAL			
[b] **Patients who are anti-coagulated with warfarin or LMWH with life-threatening bleeding that requires emergent surgical intervention**	**Adults & pediatrics:** 40-90 mcg/kg IV bolus times one dose; subsequent doses of rVIIa indicated for clinical signs of persistent bleeding, or not to maintain a normal PT/INR (round off to 1200 mcg increments)	Concomitant FFP 15-20 mL/kg, and 10 mg vitamin K IV infused over 20 minutes	INR/PT, aPTT, fibrinogen, D-dimer, FSP, CBC, before and after rVIIa,
Patients with liver failure with coagulopathy or those with excessive anti-coagulation who requires emergent invasive procedures but their PT is not reversed by aggressive replacement therapy or those who cannot tolerate conventional therapy (e.g. fluid issues)	**Adults:** 20 mcg/kg IV bolus times one dose; subsequent doses of rVIIa indicated for clinical signs of persistent bleeding, or not to maintain a normal PT/INR **Pediatrics:** 40 mcg/kg IV bolus times one dose; subsequent doses of rVIIa indicated for clinical signs of persistent bleeding, or not to maintain a normal PT/INR (round off to 1200 mcg increments)	Concomitant FFP 15-20 mL/kg, and 10 mg vitamin K IV infused over 20 minutes	INR/PT, aPTT, fibrinogen, D-dimer, FSP, CBC, before and after rVIIa,

NOTE: Given the cost of the drug, consideration should be given to rounding the dose to vials size when clinically appropriate.

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PLATELET DISORDERS WITH LIFE-THREATENING BLEEDING UNRESPONSIVE TO PLATELET TRANSFUSION (HEMATOLOGY APPROVAL REQUIRED)			
Glanzmann thrombasthenia refractory to platelet transfusion	**Adults and pediatrics:** 50-100 mcg/kg IV times one and may repeat until hemostasis is achieved. (Round off to 1200 mcg increments). Duration of therapy depends on hemostatic response and at the discretion of hematology attending.	Administer aminocaproic acid, continue aggressive platelet transfusion to keep greater than 50 x 10^9/L; PRBC transfusion, FFP, cryoprecipitate.	PT, aPTT, fibrinogen, D-dimer, FSP, CBC, before and prior to rVIIa.
DAH in BMT settings who develop early DAH during engraftment period or within 30 days post transplant	**Adults & pediatrics:** 90 mcg/kg IV bolus times one within 24hours once the diagnosis is made. If there is clinical response, may repeat times one (round off to 1200 mcg increments). Consult hematology for further dosing if needed.	Administer aminocaproic acid, continue aggressive platelet transfusion to keep greater than 50 x 10^9/L; PRBC transfusion, FFP, cryoprecipitate.	PT, aPTT, fibrinogen, D-dimer, FSP, CBC, before and prior to rVIIa.

NOTE: Given the cost of the drug, consideration should be given to rounding the dose to vials size when clinically appropriate.

RECOMBINANT FACTOR FVIIA (RFVIIA) DOSING GUIDELINES IN THE TREATMENT OF NON-HEMOPHILIAC BLEEDINGS IN VARIOUS CLINICAL SETTINGS

INDICATIONS	RFVIIA DOSE	OTHER MEASURES	MONITORING PARAMETERS
OTHER HEMATOLOGIC DISORDERS (ADULT HEMATOLOGY APPROVAL REQUIRED)			
Type III von Willebrand disease with inhibitor against VWF	**Adults:** 90 mcg/kg IV bolus or 100 mcg/kg bolus x1 followed by 20 mcg/kg CI until hemostasis is achieved. (Round off to 1200 mcg increments). Duration of therapy depends on hemostatic response and at the discretion of hematology attending.	Combination of tranexamic acid may be considered to maximize bleeding control	vWF level, PT, aPTT, fibrinogen, D-dimer, FSP, CBC, before and after rVIIa
CONGENITAL FACTOR VII DEFICIENCY (HEMATOLOGY APPROVAL REQUIRED)			
FVII activity < 25% and at risk for neuro, cardiothoracic, ophthalmologic bleed who do not respond to or cannot tolerate FFP volume infusion	**Adults & pediatrics:** 10-30 mcg/kg IV bolus q 4-6 hours until hemostasis is achieved. (Round off to 1200 mcg increments). Consult hematology for further dosing.	Continue FFP infusion if tolerated	FVII activity level, PT, aPTT, fibrinogen, D-dimer, FSP, CBC, before and after rVIIa,

PT=prothrombin time; aPTT=activated partial thromboplastin time; CI=continuous infusion; GI=gastrointestinal; PRBC=packed red blood cell; FFP=fresh frozen plasma; INR=international normalized ratio; LMWH= low molecular weight heparin; FSP=fibrin split products; BMT=bone marrow transplant; DAH=diffuse alveolar hemorrhage;

[a] Uncontrolled hemorrhage is defined as ongoing bleeding and coagulopathy despite surgical intervention and PRBC transfusion . Please refer to specific protocol for detailed information)

[b] rVIIa is NOT recommended in patients with minimal or no active bleeding or no indication of risk of continued intracranial hemorrhage. Treatment of 10 mg vitamin K IV or SQ and/or FFP infusion should be considered the first choice.

[c] Cost per dose is calculated based on 70 kg bodyweight charged by Shands acquisition cost(1.2 mg vial = $972; 4.8 mg vial=$3888). All rVIIa dosing calculation should be based on actual body weight and doses should be rounded off to 1,200 mcg increments.

[d] Acidosis (e.g. pH from ↓ 7.4 to 7.0) was shown to reduce the activity of rVIIa by > 90% or of FVIIa/TF by > 60%. (TF=tissue factor)

[e] Hypothermia (e.g. body temperature ↓ from 37C to 33°C) was shown to reduce the activity of FVIIa/TF by > 20%.

[f] Invasive procedures include ICP monitor placement, thoracentesis, tissue biopsies, large bore central line placement such as subclavian)

NOTE: Given the cost of the drug, consideration should be given to rounding the dose to vials size when clinically appropriate.

FACTOR REPLACEMENT (VIII and IX)

SUMMARY FACTOR VIII DOSING RECOMMENDATIONS

ASSUMPTIONS

1 unit of Factor VIII is defined as the amount in 1 mL of plasma.
1 unit of Factor VIII will raise the level in 1 mL of plasma from 0% to 100%.
Half-life is 8-12 hours.
Plasma volume is estimated at 40 mL/kg.

DOSING

Factor VIII loading dose = (desired peak FVIII level minus (-) the current level of FVIII) multiplied (x) plasma volume.
½ the loading dose should be repeated q8-12 hours to maintain desired peak levels.
Actual dosing should be modified based on trough and peak Factor VIII levels, as well as the clinical situation.
Continuous infusion of Factor VIII can also be considered.

Example: 70 kg man with severe hemophilia A and a major intracranial bleed.
Factor VIII loading dose = (100% minus 0%) x 2800 mL = 2800 units
To maintain peak levels at 100%, 1400 units should be given Q8-12H

Reference: Coagulation Product Review, University of Florida 1999.

SUMMARY FACTOR IX DOSING

ASSUMPTIONS

1 unit of Factor IX is defined as the amount in 1 mL of plasma.
2 units of infused Factor IX will raise the level of 1 mL of plasma from 0% to 100%. Since Factor IX equilibrates equally with the extravascular volume, it has a volume of distribution (Vd) twice that of Factor VIII.
Half-life is 12-24 hours.
Plasma volume is estimated at 40 mL/kg.
Based on the above, replacement dosing of FIX will be twice that calculated for FVIII replacement.

DOSING

Factor IX loading dose = [(desired peak FIX level - the current level of FIX) x Plasma Volume] x 2
Half of the loading dose should be repeated q 12-24 hours to maintain desired peak levels.
Subsequent dosing should be modified based on trough and peak Factor IX levels as well as the clinical situation.
Continuous infusion of Factor IX can also be considered.
Dose 20% higher when using recombinant product as recovery is less than 100%.

Example: 70 kg man with severe hemophilia B and a major intracranial bleed
Factor IX loading dose = (100% minus 0%) x 2800 mL x 2 (= 5600 units)
To maintain peak levels at 100%, 2800 units should be given q 12-24 hours.

If a recombinant FIX product is used these doses should be multiplied by 120% to increase doses by twenty percent.

Reference: Coagulation Product Review at the University of Florida, 1999.

FACTOR VIII INHIBITORS

DIAGNOSIS OF FACTOR VIII AUTOANTIBODIES

Partial thromboplastin time prolonged; prothrombin time normal; thrombin time normal.
Exclude heparin contamination of the sample.
Mix patient plasma with normal plasma and do PTT on mixture.
Continual prolongation of PTT supports the diagnosis of an inhibitor.
Also check after 60 min incubation at 37^0 C.
No correction by platelets or phospholipid (excludes lupus anticoagulant).
Plasma must be platelet-poor.
Factor VIII is decreased; other factors normal.
Others may appear decreased if high titer F VIII inhibitor is present.
Bethesda assay quantifies inhibitor.
BU is defined as the reciprocal of the patient's plasma dilution that neutralizes 50% of Factor VIII.
Low titer inhibitor (low responder) <5BU.
High titer (high responder) >10 BU.

PRODUCT	COMMENT
DDAVP	Useful only in patients with low titer inhibitors and mild disease.
High-dose human factor VIII	Useful only in patients with low titer (<5 B.U.) inhibitors. In patients with a history of a high titer inhibitor, use only in limb and life threatening bleeds.
Recombinant Factor VIIa (NovoSeven®)	Does not produce DIC and can be used with antifibrinolytic agents. Can also be used for Factor IX inhibitors. Questionable thrombotic risk in older patients with established atherosclerotic disease. Short half-life.
Activated Prothrombin Complex (FEIBA®/Autoplex®)	Risk of DIC and thrombosis

TREATMENT OF FACTOR VIII INHIBITORS

TITER BETHESDA UNITS (BU)	PRODUCT	TREATMENT APPROACH
Less than 5 BU, not limb or life-threatening bleeding	1.DDAVP 2.Recombinant human Factor VIII	1. Dose 0.3 micrograms/kg 2. Dose 50 - 100 units/kg or greater (dependent on inhibitor level) have been used if low responding inhibitor
5 - 30 BU	1.Recombinant Factor VIIa (NovoSeven®) 2. APCCs (FEIBA®/Autoplex®)	1. Dose 90 micrograms/kg every 2-3 hours 2. Dose 50 -75 units/kg every 8-12 hours
Greater than 30 BU, and serious bleeding	1. Recombinant F VIIa 2. APCCs (FEIBA®/Autoplex®)	1. Dose 90 units/g every 2-3 hours 2. Dose 50 - 100 units/kg every 8-12 hours

Reference: Lloyd Jones, M, et al. *Haemophilia* 2003;9:464 - 520.