

**Regional Guidelines for off-licence use of
Recombinant Factor VIIa (Eptacog-alfa; NovoSeven®)
in acquired coagulopathy.**

Contents

- **Context**
- **Guidelines**
- **Bibliography**
- **Appendices**
 - **I Pre-admin audit form**
 - **II Post-admin audit form**
 - **III Mode of Action of Activated Factor VIIa**
 - **IV Membership of the Working Group**

**ACTIVATED FACTOR VIIa WORKING GROUP
NORTHERN IRELAND ADVISORY COMMITTEE ON BLOOD SAFETY**

AUGUST 2007

Context for Regional Guidelines for off-licence use of Recombinant Factor VIIa (NovoSeven®) in acquired coagulopathy

Recombinant Factor VIIa has proven potential to save lives in some cases of severe haemorrhage. Severe haemorrhage very common but in many cases Recombinant Factor VIIa would not be expected to be beneficial.

Recombinant Factor VIIa is not a replacement for appropriate attempts at haemostasis e.g surgery or embolization.

Possibility that Recombinant Factor VIIa might be used in unfavourable conditions in order to “do something” in a life-threatening emergency. Potential for inappropriate use high - and with a cost per dose of £5000 approx. there is possibility of significant misuse of resources.

When used appropriately Recombinant Factor VIIa may result in decrease in exposure of patients to donated blood (which may be important in terms of transmissible diseases and organ failure related to massive transfusion of blood).

Due to funding mechanism with NIBTS, use of Recombinant Factor VIIa would not expect a reduction in costs due to reduced blood use (potentially large reduction in blood use but only in a relatively small number of patients).

Usage of Recombinant Factor VIIa at present running at about 50 cases per year (1-2 doses per case).

Funding and prescribing arrangements across NI variable. At present, Recombinant Factor VIIa may not be available in some Trusts. In others it is available but use will result in budget overspend. In one Trust a limited amount of use per year has been approved and funded.

Haematologists unhappy with role as gatekeeper and accessing drug via Haematology may delay administration in some (appropriate) situations. Regional guidelines aim to replace gatekeeping role, maximize benefit but continue to discourage inappropriate use of Recombinant Factor VIIa.

To achieve the above, guidelines are complemented by pre-administration checklist and prescription sheet and a post administration audit form. Haemovigilance, N.I. Intensive Care Society and Haematology have agreed to be involved in reviewing audit data - quarterly for the first year.

Regional Guidelines for off-licence use of Recombinant Factor VIIa (Eptacog-alfa; NovoSeven®) in acquired coagulopathy.

Introduction.

Recombinant factor VIIa (rFVIIa) is licensed for use in congenital and acquired Haemophilia (in patients with high antibody titres), FVII deficiency and Glanzmann's Thrombaesthesia.

Anecdotal experiences and subsequent case series have reported it to be useful (outside licence) for treatment of patients with continuing severe haemorrhage despite attempts to correct coagulopathy and optimal management (eg surgical, radiological) addressing haemostasis.

There is some evidence that appropriate use of rFVIIa reduces the amount of blood products needed and the duration of subsequent mechanical ventilation and other critical care support (perhaps by a reduction in the incidence/severity of Transfusion-Related Acute Lung Injury and other complications).

Mode of action.

See appendix III.

Important considerations.

It is imperative that every effort is made to correct deficiencies in platelets and coagulation factors by administering appropriate platelet, plasma and cryoprecipitate/fibrinogen concentrate prior to treatment with rFVIIa.

It is much less likely to be effective if used late (eg "last resort") in massive transfusion and should not be administered to patients with no significant chance of survival.

- This is an off-licence use of rFVIIa and therefore serious consideration should be given to obtaining relative's assent prior to use if possible. (It is unlikely that patients will be competent to give their consent).
- There is a theoretical risk of inducing thrombosis in at-risk groups.
- Recombinant rFVIIa should be used in only a tiny proportion of haemorrhaging patients.
- Its use needs to be tracked by a regional audit system (see below)

Indications (any of following).

1. Ongoing clinically significant haemorrhage despite appropriate attempts to achieve surgical control of bleeding, and after correction of other clotting factor/platelet deficiencies (see preconditions) and adherence to regional guidance – *Better Blood Transfusion* (CREST).
2. Severe obstetric haemorrhage requiring consideration of internal iliac artery ligation, uterine artery embolisation, or hysterectomy in the setting of optimal blood product support.

Typical clinical scenarios under indications 1 & 2 would include patients who have

- *Continuing brisk blood loss (>200ml/hr) for >5 hours after attempting local control measures (and no foreseeable further mechanical control options), and optimal blood product support.*
- *lost six units of blood (based on 70kg – adjust appropriately according to estimated lean body mass) during a 2-3 hour period, or*
- *lost 4-6 units rapidly in the perioperative period*
- *lost more than two thirds of their blood volume within a 24 hour period.*

These indications assume normal haemoglobin levels. A lower starting haemoglobin might require appropriate adjustment.

3. Severe haemorrhage, refractory to local control, in patient who refuses/would refuse blood products but would accept recombinant blood factors. Administration in these patients may need to be earlier in the course of events, because transfusion is prohibited.

Cautions

- Severe sepsis and/or sepsis-related coagulopathy (theoretical increased risk of DIC)
- Crush injury/parenchymal brain injury (theoretical risk of intravascular thrombosis)
- Recent microvascular surgery eg free flap procedures
- History of thromboembolic disease, severe atherosclerosis, ischaemic stroke

Contraindications

- “Last ditch” therapy
- Gastrointestinal bleeding associated with end-stage liver disease
- Allergy to mouse, hamster or bovine proteins

Pre-conditions for Use

Two consultants must agree to use of rFVIIa. Both should be involved in the care of the (haemorrhaging) patient.

All standard measures for the management of massive haemorrhage will have been undertaken before the potential use of rFVIIa including:

1. Adequate correction of hypovolaemia.
2. Attempts to correct coagulation. This should include obtaining fibrinogen levels of > 0.5 g/L and platelets >50 x10⁹/l or prior empiric administration of platelets, FFP and/or cryoprecipitate. In specific patients this will also include the adequate reversal of anticoagulation (heparin or warfarin).
3. Attempts to correct acidosis – (aim for pH =7.20 or higher - poor response to rFVIIa if pH <7.1)
4. Administration of calcium (as per CREST guidelines for massive transfusion)
5. Attempts to prevent and/or correct hypothermia (rFVIIa works at any temperature but other components of the haemostatic system do not).
6. Attempts to achieve Haematocrit of 0.24 (facilitates clot formation)

7. Consider use of other agents such as tranexamic acid, aprotinin or DDAVP.

Arrangements for administration.

It is important that rFVIIa is available to clinician rapidly at any hour of the day. It would be most appropriate for stocks of this agent to be held in Blood Bank if this is possible under local arrangements. *If this is not possible, rapid availability at all times should be the prime consideration in deciding the place of storage and issuing arrangements for factor rFVIIa.*

A written record of telephone requests for rFVIIa should be made by Blood Bank (or surrogate) and kept by Haemovigilance practitioner in issuing hospital. This will be an important part of the audit of rFVIIa use.

Dosage and administration

- Initial dose is 90 -100mcg/kg rounded up to next whole vial.
- Give as a slow IV bolus over 2-5 minutes.
- Do not mix rFVIIa with other infusion solutions.
- Response should be assessed on clinical grounds ie reduction or cessation of haemorrhage.
- If severe bleeding is ongoing, a second dose of 90-100 mcg/kg may be given if appropriate after 1 hour (2 hours maximum).
- No further doses should be administered under any circumstances during a single bleeding episode. *If patient has a separate bleeding episode later in their illness, the use of rFVIIa may be considered again applying the above principles.*

Monitoring response

1. Record the trend in blood loss
2. Record blood product use & rate of use.
3. Continue to monitor FBP and coagulation screen including D-dimers. *The dose of recombinant Factor VIIa is empirical and not based on laboratory monitoring but on clinical effect in haemophiliac patients. The prothrombin time and APTT should decrease (the former dramatically) but these are not useful measures of the haemostatic effects of recombinant Factor VIIa*

Safety issues.

Remain alert to the theoretical possibility of undesirable thrombotic events (e.g. deep venous thrombosis, pulmonary embolism, thrombotic cerebro-vascular accident). This may require a lower than normal threshold for appropriate investigations.

Audit.

The Pre-administration Audit & Prescription sheet for rFVIIa use must be completed before the product is released for use.

Bibliography

Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, de Moerloose P: Prolonged treatment of massive postpartum haemorrhage with recombinant factor VIIa: case report and review of the literature.
BJOG 2004, 111:284-287.

Boffard KD, Riou B, Warren B, Iau P, Rizoli SB, Rossaint R, Axelsen M, Kluger Y: Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients. Two parallel randomized, placebo-controlled, double-blind clinical trials.
J Trauma 2005, 59:8-15.

Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez Abraldes J, Fabricius S, Erhardtsen E, de Franchis R, European Study Group on rFVIIa in UGI Haemorrhage: Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial.

Bouwmeester FW, Jonkhoff AR, Verheijen RH, van Geijn HP: Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII.
Obstet Gynecol 2003, 101:1174-1176.

Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS: Blood transfusions correlate with infections in trauma patients in a dose-dependent manner.
Am Surg 2002, 68:566-572.

Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Surviving Sepsis Campaign Management Guidelines Committee, *et al.*: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.
Crit Care Med 2004, 32:858-873.

DeLoughery TG: Coagulation defects in trauma patients: etiology, recognition, and therapy.
Crit Care Clin 2004, 20:13-24. [

Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, Scalea TM: Factor VIIa for correction of traumatic coagulopathy.
J Trauma 2004, 57:709-718.

Erhardtsen E: Ongoing NovoSeven trials.
Intensive Care Med 2002, 28(Suppl 2):S248-S255.

Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, Buller HR, Levi M: Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial.
Lancet 2003, 361:201-205.

Gabriel DA, Li X, Monroe DM 3rd, Roberts HR: Recombinant human factor VIIa (rFVIIa) can activate factor FIX on activated platelets.
J Thromb Haemost 2004, 2:1816-1822.

Harrison TD, Laskosky J, Jazaeri O, Pasquale MD, Cipolle M: 'Low-dose' recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage.
J Trauma 2005, 59:150-154.

Hoffman M, Monroe DM 3rd: The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis.
Dis Mon 2003, 49:14-21.

Hoyt DB: A clinical review of bleeding dilemmas in trauma.
Semin Hematol 2004, 41(1 Suppl 1):40-43.

Karkouti K, Beattie WS, Wijeyesundera DN, Yau TM, McCluskey SA, Ghannam M, Sutton D, van Rensburg A, Karski J: Recombinant factor VIIa for intractable blood loss after cardiac surgery: a propensity score-matched case-control analysis.
Transfusion 2005, 45:26-34.

Levi M, Peters M, Buller HR: Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review.
Crit Care Med 2005, 33:883-890.

Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM: Blood transfusion, independent of shock severity, is associated with worse outcome in trauma.
J Trauma 2003, 54:898-905.

Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M: Recombinant activated factor VII for adjunctive hemorrhage control in trauma.
J Trauma 2001, 51:431-438.

Martinowitz U, Michaelson M, Israeli Multidisciplinary rFVIIa Task Force: Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force.
J Thromb Haemost 2005, 3:640-648.

Meijer K, Hendriks HG, De Wolf JT, Klompmaker IJ, Lisman T, Hagenaars AA, Slooff MJ, Porte RJ, van der Meer J: Recombinant factor VIIa in orthotopic liver transplantation: influence on parameters of coagulation and fibrinolysis.
Blood Coagul Fibrinolysis 2003, 14:169-174.

Moscardo F, Perez F, De La Rubia J, Balerdi B, Lorenzo JI, Senent ML, Aznar I, Carceller S, Sanz MA: Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII.
Br J Haematol 2001, 114:174-176.

Meng ZH, Wolberg AS, Monroe DM 3rd, Hoffman M: The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients.

J Trauma 2003, 55:886-891.

O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM: Thromboembolic adverse events after use of recombinant human coagulation factor VIIa.

JAMA 2006, 295:293-298.

Raivio P, Suojäranta-Ylinen P, Kuitunen AH: Recombinant factor VIIa in the treatment of postoperative hemorrhage after cardiac surgery.

Ann Thorac Surg 2005, 80:66-71.

Raux M, Chiche L, Vanhille E, Riou B: Recombinant activated factor VII to control massive postoperative bleeding after septic aortobifemoral grafting.

Eur J Anaesthesiol 2005, 22:805-807

Segal S, Shemesh IY, Blumenthal R, Yoffe B, Laufer N, Ezra Y, Levy I, Mazor M, Martinowitz U: Treatment of obstetric hemorrhage with recombinant activated factor VII (rFVIIa).

Arch Gynecol Obstet 2003, 268:266-267.

Shander A, Goodnough LT, Ratko T, Matuszewski KA, Cohn S, Diringer M, Edmunds H, Lawson J, MacLaren R, Ness P, *et al.*: Consensus recommendations for the off-label use of recombinant human factor VIIa (NovoSeven®) therapy.

Pharmacy & Therapeutics 2005, 30:644-658.

Spahn DR, Rossaint R: Coagulopathy and blood component transfusion in trauma.

Br J Anaesth 2005, 95:130-139.

Stehling LC, American Society of Anesthesiologists Task Force on Blood Component Therapy: Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy.

Anesthesiology 1996, 84:732-747.

Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR.

Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding – a European perspective.

Critical Care 2006, 10:R120

Vivien B, Langeron O, Morell E, Devilliers C, Carli PA, Coriat P, Riou B: Early hypocalcemia in severe trauma.

Crit Care Med 2005, 33:1946-1952.

Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C: Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity.

J Trauma 1998, 44:846-854.

Date

Hospital

Patient Label

**PRE-ADMINISTRATION AUDIT & PRESCRIPTION FORM
for Recombinant Factor VIIa
*Must be completed before administration of product***

Indication (*must tick at least one of the following*)

- Ongoing clinically significant haemorrhage (see indications) after;
- appropriate attempts to achieve control of bleeding surgically
 - correction of other clotting factor/platelet deficiencies (see preconditions)
 - adherence to regional guidance – *Better Blood Transfusion* (CREST).
- Severe obstetric haemorrhage requiring consideration of internal iliac artery ligation, uterine artery embolisation, or hysterectomy in the setting of optimal blood product support.
- Severe haemorrhage, refractory to local control, in patient who refuses/would refuse blood products but would accept recombinant blood factors

Contra-indications (*A tick in any box is a definite contra-indication for use of rFVIIa*).

- “Last ditch” therapy
- Gastrointestinal bleeding associated with end-stage liver disease
- Allergy to mouse, hamster or bovine proteins

Cautions

(A tick in one or more boxes requires a risk-benefit assessment by an appropriate senior doctor before administration of rFVIIa).

- Severe sepsis and/or sepsis related coagulopathy
- Crush injury/parenchymal brain injury
- Recent microvascular surgery
- History of thromboembolic disease/severe atherosclerosis/ischaemic stroke

Optimisation of the patient. The following have been actively pursued (*must tick all*):

- Correction of acidosis
- Optimal replacement of coagulation factors and platelets
- Optimal strategies aimed at normalising temperature
- No further local control measure feasible at this stage

Prescribing Consultant 1 Name _____ Signature * _____

Prescribing Consultant 2 Name _____ Signature** _____

* must be signed at time of request for rFVIIa

** may be signed retrospectively

**POST-ADMINISTRATION AUDIT FORM
for Recombinant Factor VIIa**

Must be completed after administration of product

Part A *(To be completed by local Haemovigilance Practitioner between 48 hours and 7 days after administration)*

Hospital _____ Prescribing Consultants 1 _____ 2. _____

| |
|---|
| <i>Patient details</i> Hosp No Address DOB |
|---|

Administration of the first dose of Recombinant Factor VIIa

Date

Time

Dose

Administration of the second dose of Recombinant Factor VIIa

Date

Time

Dose

Dose of Recombinant Factor VIIa returned to source of supply (blood bank/pharmacy etc) _____

Patient outcome at 48 hours [survivor / non survivor]

Haemovigilance Practitioner Name (print) _____ Signature _____

+++++

Part B *(To be completed by prescribing consultants(s) 28 days after administration)*

Outcome at 28 days [survivor / non survivor]

Is patient still in critical care unit [yes / no]

Final diagnosis _____

In retrospect was administration of Recombinant Factor VIIa appropriate
[yes / no]

Prescribing Consultant 1 Name (print) _____ Signature _____

Prescribing Consultant 2 Name (print) _____ Signature _____

Appendix III

An Introduction to the Mode of Action of Recombinant VIIa

The historical division of the coagulation scheme into extrinsic and intrinsic pathways is helpful to guide laboratory investigation but fails to explain all facets of the dynamic in vivo coagulation system. Extensive work by many teams has led to the development of the cell based model of haemostasis. Hoffman's ⁽¹⁾ research group have devised a cell based model which portrays coagulation occurring on cell surfaces in a series of three overlapping steps termed Initiation; Amplification and Propagation.

There is basal low level thrombin generation activity, the Initiation phase, occurring at all times outside the vasculature but Amplification does not occur unless there is damage to the vessel wall. Following vessel wall assault there is exposure of Tissue Factor (TF) and subsequent binding to Factor VIIa. This leads to activation of both Factor X \rightarrow Xa and IX \rightarrow IXa. The FXa generated can combine with FVa to form a prothrombinase complex which cleaves Factor II (Prothrombin) to Thrombin (IIa). Vessel wall damage also permits the passage of platelets, FVIII and v WF, amongst others, which come into contact with the limited amount of thrombin being generated on the cell surface.

The thrombin generated has multiple roles including cleavage and activation of FVIII from vWF, activation of platelets with subsequent conformational changes, further activation of FV and activation of FXI to FXIa. This subsequently leads to activated platelets with multiple adherent activated cofactors. In the propagation phase, the majority of the generated thrombin is produced on the activated platelet surface. This is brought about by the formation of a FVIII/FIX complex that activates FX \rightarrow Xa which then binds to FVa. This then leads to the cleavage of Prothrombin with consequent enhanced thrombin generation. Factor XIII is activated by thrombin and leads to enhanced clot stability by cross linking of the fibrin strands and Thrombin Activatable Fibrinolysis Inhibitor (TAFI) is also stimulated by the high generation of thrombin, with subsequent down regulation of fibrinolysis.

Mechanisms of Action of Recombinant VIIa

Recombinant VIIa functions by both TF dependant and independent mechanisms. Despite low affinity, it binds to activated platelets in pharmacological doses independent of TF pathways and causes activation of Factor X. There is also concomitant enhanced TF occupancy with amplification of downstream effects. These dual effects lead to "supranormal" boosts in thrombin and potential subsequent clot formation. Clots formed under such conditions of high thrombin activity have been shown to have a varying architecture which is stronger and more resistant to fibrinolysis.

Recombinant VIIa has an identical amino acid sequence to plasma derived FVIIa. It is available as a virally inactivated, white lyophilised powder available in single use vials. It should be reconstituted with sterile water for injection. Following

reconstitution it should be used within 3 hours. Dosing schedules vary according to the indication for usage. For contraindications and precautions please consult product literature. Adequate haemostatic support, in the form of FFP, Cryoprecipitate and platelets as appropriate, needs to be optimised prior to usage. There is decreased efficacy in the settings of acidosis

Current European Union Licences for Recombinant VIIa as of March 2006 are as follows:

Congenital Haemophilia with Inhibitors.

Acquired Haemophilia

Glanzmann's thrombasthenia

Congenital Factor VII deficiency.

Please consult Northern Ireland Recombinant VIIa guidelines prior to the usage of this product.

References

A Cell-based model of coagulation and the role of factor VIIa. Hoffmann M. *Blood Reviews* (2003) Vol 17. Suppl 1. Pages S1-S5

APPENDIX IV

MEMBERSHIP OF THE ACTIVATED FACTOR VIIa WORKING GROUP

Chairman: Dr Gavin Lavery, Director Critical Care Services, Royal Hospitals

Mr Paul Blair, Director of Trauma, Royal Hospitals

Ms Rhona Fair, Assistant Director, Pharmacy Department, Royal Hospitals

Dr Frank Jones, Consultant Haematologist, Belfast Link Laboratories

Dr Charlie McAllister, Consultant Intensivist, Craigavon Area Hospital

Dr John McAteer, Consultant Anaesthetist, Ulster Hospital

Dr Donal McLornan, SpR Haematology, Belfast City Hospital

Ms Andrée McCollum, Director of Pharmaceutical Services, Eastern Health & Social Services Board

Mr Desmond Meredith, Patient Representative, Health & Social Services Council

Dr Joanne Murdock, Consultant Transfusion Medicine, Northern Ireland Blood Transfusion Service

Dr Mary Murnaghan, Consultant Obstetrics & Gynaecology, Mater Hospital

Ms Shirley Murray, Regional Co-ordinator for Haemovigilance, Belfast Link Laboratories

Dr Denis O'Keefe, Consultant Haematologist, Belfast City Hospital

Dr John Trinder, Lead Clinician, ICU, Ulster Hospital

Secretariat: Mr Johnny Wright, Department of Health, Social Services and Public Safety