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CCaNNI 003

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**Standard off licence use of Recombinant Factor VIIA (Eptacog-
alfa; Novoseven®) in acquired coagulopathy**

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Standard off licence use of Recombinant Factor VIIA (Eptacog-alfa; Novoseven®)
in acquired coagulopathy **Issued April 2008**

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Standard off- licence use of Recombinant Factor VIIA (Eptacog-alfa; Novoseven®) in acquired coagulopathy

1. The purpose/objective of the standard/guideline

Appropriate use of agent in clinical situation where it would be of benefit, while avoiding situations where use might be expected to result in (i) patient harm or (ii) misuse of resources

2. Intended target population

As listed in indications

3. Time scale for implementation

For immediate implementation

4. Resource Implications

5. Financial disclosures/conflicts of interest

None

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

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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

1.0 Context

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.

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

When used appropriately Recombinant Factor VIIa may result in decreased 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 the funding mechanism for NI Blood Transfusion Service, use of Recombinant Factor VIIa would not expect a reduction in costs due to reduced blood use (potentially large reduction in blood use but in only a relatively very small number of patients).

In the past haematologists have been unhappy with role as “gatekeeper” for rFVIIa and accessing the drug by such a route might delay administration in some (appropriate) situations. Regional guidelines aim to replace the gatekeeping role, maximize benefit but continue to discourage inappropriate use of Recombinant Factor VIIa.

To achieve the above, the guidelines are complemented by a pre-administration checklist and prescription sheet.

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

2.0 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 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. Clinical experience over several years has led local clinicians to value its use under certain (relatively uncommon) situations.

An (as yet) unpublished met analysis of placebo controlled trials involving patients with intracranial haemorrhage, trauma, liver surgery or cardiac surgery concluded that off-licence use of rFVIIa for haemorrhage increased the risk of arterial thrombo-embolic events (5.6% vs 3%). Massive obstetric haemorrhage cases were not included. Nevertheless, European SPC for Novoseven now includes the statement "safety and efficacy of Novoseven have not been established outside the approved indications and therefore Novoseven should not be used [outside licence]". In view of this, any potential benefit from the use of rFVIIa must be balanced against the now recognized increased risk of thrombo-embolic events.

3.0 Mode of action

See appendix III.

4.0 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 (e.g. "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 informed assent prior to use if possible. (It is unlikely that patients will be competent to give their consent).
- An as yet unpublished meta-analysis has shown that off license use of rFVIIa for haemorrhage (excluding obstetric haemorrhage) increased the risk of arterial thrombo-embolic events (5.6% vs. 3%).

5.0 Indications

Clinical use should follow a risk benefit analysis of the potential to prevent ongoing uncontrolled haemorrhage versus the danger of thrombotic complications.

1. Severe obstetric haemorrhage requiring consideration of internal iliac artery ligation, uterine artery embolisation, or hysterectomy in the setting of optimal blood product support.
2. 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 use of Blood in Northern Ireland - March 2009](#) (GAIN/CREST).

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.

6.0 Cautions

- History of thromboembolic disease, severe atherosclerosis, ischaemic stroke. Recent evidence suggests such patients may be almost twice as likely to develop thrombotic complications (see above)
- 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 e.g. free flap procedures

7.0 Contraindications

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

8.0 Pre-conditions for Use

Two consultants must agree to use of rFVIIa. Both should be actively involved with 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 > 50x10³ 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 <7.2)
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.

9.0 Arrangements for administration

It is important that rFVIIa is available to clinicians 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 the Haemovigilance practitioner in issuing hospital. This will be an important part of the audit of rFVIIa use.

10.0 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.

11.0 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. *The dose of recombinant Factor VIIa is empirical and not based on laboratory monitoring but on clinical effect in haemophilic 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*

12.0 Safety issues

Remain alert to the 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.

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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

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 → Xa and IX → 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 vWF, 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 → 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

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