NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Recombinant Factor VIIa, Extended Use

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

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Change of Record

Date	Author	Nature of Change	Reference

Protocol for Extended Use of Recombinant Factor VIIa (rFVIIa) (excluding ECMO)

Recombinant FVIIa (rFVIIa) has proven efficacy and is licensed for use to control or prevent bleeding in acquired and inherited haemophilia patients with inhibitors who are unresponsive to conventional Factor VIII or IX replacement.[1-3] There are a number of case reports and case series advocating its potential usefulness in non haemophilia patients with intractable bleeding,[4-13] or even as prophylaxis prior to high blood-loss surgery.[14] However, its efficacy in these circumstances has been examined in several randomised controlled trials, none of which showed any benefit [and may in fact demonstrate harm], and rFVIIa thus remains unlicensed for such indications. It is also very expensive.

Nevertheless there may be a place for considering its use *in extremis* to control bleeding in certain situations when other measures have failed.

It is imperative that every effort is made to correct deficiencies of platelets and coagulation factors by administering appropriate platelet, plasma and cryoprecipitate prior to considering treatment with rFVIIa. Attempts should also be made to correct acidosis and hypothermia as both may adversely affect haemostasis *in vivo*, and decrease the efficacy of rFVIIa should it be given.

Please note: a meta-analysis demonstrated a significant increase in arterial events in rFVIIa recipients compared to placebo, including more deaths. As a result, the Summary of Product Characteristics for the available commercial product (NovoSeven) now specifically states that it should not be used for un-licensed indications, and the Scotland and Northern Ireland Haemophilia Directors Group have issued a statement recommending that this guidance should be followed. Requesting clinicians should take note of this, and be absolutely clear that rFVIIa must only be used when the likelihood of survival without it is very small, and any benefit outweighs the potential for harmful side effects. It is likely that such indications will be rare.

Appropriate advice should be sought from the on-call consultant haematologist, but the final decision to use the drug must be taken by the treating consultant. Its use and any prior discussions should be documented in the patient case notes reflecting the perceived threat to life if rFVIIa is not used. The attached audit form must be completed (Appendix A) and returned to the HTC chair (or designated deputy) to permit an audit trail.

Possible indications for treatment with rFVIIa:

<u>Life Threatening Bleeding</u>

Clinical situation

- Life threatening bleeding due to surgery (e.g. vascular, cardiac) or trauma (e.g. unstable pelvic fracture) or due to an acute spontaneous bleed (e.g. upper GI bleeding) which persists **despite** appropriate blood product replacement and surgical intervention.[6-9,14]

Patients

- Any patient with bleeding as described
- Patients who are Jehovah's witnesses who have a massive blood loss.

- Patients with significant thrombocytopenia who are bleeding despite platelet transfusion or in the presence of platelet refractoriness.[10,11] (although it should be noted that in this setting the efficacy of rFVIIa may be impaired).
- A separate protocol for the use of rFVIIa exists for patients undergoing ECMO at RHSC

Relative contra-indications

The mechanism of action of rFVIIa probably relates to a supra-physiological surge of thrombin generation. For this reason, rFVIIa may be unsuitable in patients with atherosclerosis or major crush injury (particularly brain) because of a theoretical higher risk of thrombotic manifestations.

How to obtain rFVIIa

rFVIIa stock will be held within the haematology laboratory. All patients being considered for rFVIIa treatment must be discussed by the treating consultant with a consultant haematologist. NO rFVIIa will be issued without such discussion.

Dosing and administration

An initial dose of 90 μg/kg rFVIIa by slow IV bolus (3-5 mins) may be repeated after 1-2 hours if there is still significant blood loss. A further dose of 90 μg/kg can be considered if bleeding decreases but does not stop.

Efficacy

The primary measure of haemostatic efficacy is the clinical assessment of bleeding rate (i.e. stopped, decreased or unchanged). Clinical benefit is often seen within 10-20 minutes of rFVIIa administration. A reduction in blood and blood products use is a reasonable secondary measure of haemostatic efficacy. Review of 40 cases of off-license use for surgery or trauma bleeding in the UK has demonstrated cessation or decreased bleeding in 80% cases. However, mortality in this population of massive bleeders is still high (57%).[15]

Laboratory investigations

♦ ***Prior to administration of rFVIIa***

The efficacy of rFVIIa relies on the presence, *in vivo*, of at least modest coagulation factor levels. Therefore, a recent FBC and coagulation screen result (PT, APTT, TCT/fibrinogen and D-dimer) or TEG / TEM should be available, and appropriate amounts of FFP/platelets and cryoprecipitate should already have been administered.

♦ ***Following administration of rFVIIa***

FBC and coagulation screen should be checked 20 minutes post rFVIIa infusion.
The PT will have shortened dramatically and the APTT may shorten also. However, Factor VIIa has a short half-life and, therefore, these effects may not be long lasting and further coagulation monitoring will be required appropriate to the clinical situation.

Congenital Bernard Soulier Platelet Disorder

Recombinant factor VIIa may be appropriate treatment for acute bleeds and to cover surgery in severe cases of Bernard Soulier disorder, again this is an unlicensed indication.

Record of rFVIIa administration

As with all blood/coagulation products, details of dose and batch number should be recorded in the case notes. Details of other blood and blood products administered, results of FBC and coagulation investigations as well as a comment on apparent clinical efficacy of the rFVIIa should be recorded in the case notes. This will assist in audit of all issues of rFVIIa.

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