Queensland Health Medicines Advisory Committee (QHMAC) has considered applications to add recombinant activated factor VII (rFVIIa) to the Queensland Health List of Approved Medicines (LAM). The committee has taken the position that this item should NOT be added to the LAM but appreciates there may be specific cases (apart from its use in haemophiliac patients) where individual patient approval (IPA) is appropriate. This guide has been drafted to assist medical superintendents (or delegates) and local medicines committees in their consideration of IPA requests for recombinant activated factor VII (rFVIIa).

IPA indication

For the management of life-threatening bleeding and coagulopathy in non-haemophiliac patients who have failed to respond to conventional therapy.

Background

Recombinant activated factor VII (rFVIIa) is approved for the prevention or treatment of bleeding in haemophiliac patients with coagulation factor inhibitors. It is not registered for use in uncontrollable haemorrhage in non-haemophiliacs. However, there have been increasing reports suggesting a role for rFVIIa in the management of life-threatening bleeding in non-haemophiliac patients who have failed to respond to conventional therapy. In Israel, the Ministry of Health has approved the compassionate use of rFVIIa for patients suffering massive, life-threatening bleeding as a result of trauma or surgery. Widely agreed guidelines for the management of uncontrollable haemorrhage, coagulopathy and the role of rFVIIa do not exist. There is limited randomised controlled data on the use of rFVIIa in major haemorrhage. Current data suggests that rFVIIa use has a potential role in minimising blood product use during cessation of major haemorrhage but overall survival may not improve.

Inclusion criteria for use of rFVIIa in major haemorrhage

1. Persisting uncontrollable haemorrhage and coagulopathy (trauma, medical or peri-operative)
2. Appropriate mechanical methods of haemostasis, including surgical exploration, orthopaedic fixation and embolisation, have been addressed
3. Conventional measures to prevent and correct coagulopathy have been performed
4. Consider the administration of rFVIIa and if administered, clinically monitor the response

Exclusion criteria

1. Severe acidosis < 7.05
2. Temperature < 34 °C

After acidosis and hypothermia are corrected, NovoSeven RT® may be reconsidered for administration.
3. Gun shot wound to the head
Stepwise approach to use of rFVIIa

1. Persisting uncontrollable haemorrhage and coagulopathy (trauma, medical, or peri-operative).
   Potential patients are recognised as those suffering uncontrollable haemorrhage and coagulopathy unresponsive to conventional measures. This will usually be in the setting of a massive transfusion represented by:
   - replacement of the blood volume within a 24 hour period; this corresponds to about 70mL/kg of body weight or 5,000mL in a 70kg patient
   - replacement of 50% of the total blood volume within 3 hours
   - need for at least six Red Blood Cell (RBC) units within 4 hours in the setting of continued major bleeding
   - blood loss exceeding 150mL/min
   - need for platelet and plasma replacement

2. Appropriate mechanical methods of haemostasis, including surgical exploration, orthopaedic fixation and embolisation have been addressed.
   Any surgical and non-surgical definitive haemostasis procedures to arrest active bleeding should be attempted prior to consideration of rFVIIa administration. This may include operative surgical exploration, orthopaedic fixation and embolisation by interventional radiology.

3. Conventional measures to prevent and correct coagulopathy have been performed.
   Appropriate conventional measures to prevent and correct coagulopathy should be performed prior to consideration of rFVIIa administration. Patients considered for treatment with rFVIIa will be in a critical care environment (e.g. resuscitation room, operating theatre, ICU, angiography room). Patients should:
   - have received full resuscitation
   - have had aggressive attempts to correct acidosis and hypothermia
   - and have persisting coagulopathy despite appropriate factor and platelet replacement
   When appropriate consider the following specific measures:
   - Reversal of warfarin (vitamin K, prothrombin complex concentrate)
   - Reversal of heparin (protamine sulfate)
   - Desmopressin for Von Willebrand’s disease and patients with chronic renal failure

4. Consider the administration of rFVIIa and if administered, clinically monitor the response (An example eligibility worksheet is attached, adapted from GCH worksheet).
   If conventional therapy has failed to control the blood loss (usually 8 units of RBC’s, 8 units of FFP, and 8 units of platelets will have been given, and, if available, 10 units of cryoprecipitate if fibrinogen is low)
   AND
   Bleeding with coagulopathy continues
   AND
   All surgical and embolisation procedures have been attempted
   AND
   Consultation with appropriate clinicians in your institution has occurred to confirm optimal conventional therapy and the appropriate dosage of rFVIIa
   GIVE
   Recombinant activated factor VII (rFVIIa, Novoseven RT®)
**Recommended dosing**

For all scenarios, give an initial dose of 50 micrograms/kg. Clinical response is usually obvious within 30 minutes. If no response within 30 minutes, check for acidosis and hypothermia, and consider giving a repeat dose of rFVIIa (50 micrograms/kg). **Maximum of 2 doses to be used.**

A total dose of > 100 micrograms/kg is unlikely to achieve additional haemostasis in major haemorrhage. There is controversy in the literature as to the optimal dosing of rFVIIa in the setting of major haemorrhage and a dose response curve has not been established. However, local institutional experience suggests efficacy with lower doses initially (such as 50 micrograms/kg) and surveillance of response. In patients > 100kg, ideal body weight should be used in dosing calculations.

Having administered rFVIIa the patient should be monitored for 24 hours for subjective and objective signs of improvement and for adverse events of all blood products. Coagulation studies should also be repeated.

Use in children and pregnancy requires special consideration of the risks and benefits associated with rFVIIa.

rFVIIa should only be used where the clinician considers the benefits outweigh the risk of critical bleeding. Auditing of all patients receiving rFVIIa is to be encouraged. Use should be reported to the local Drugs and Therapeutics Committee. Clinicians should also consider reporting of cases to the Haemostasis Registry, once local Ethics Committee approval has been obtained. Hospitals should keep a local register, as this item will be subject to regular review by the Queensland Health Medicines Advisory Committee (QHMAC).

**Note:** Before rFVIIa is used in haemophilia complicated by inhibitors, acquired haemophilia, or other serious inherited bleeding disorders, further advice must be obtained from the Queensland Haemophilia Centre at Royal Children’s Hospital or Royal Brisbane & Women’s Hospital.

**Administration guidelines**

Once reconstituted, rFVIIa (Novoseven RT®) should be administered by intravenous bolus injection over a period of two to five minutes. Refer to product information for further details.

**Cost estimates**

The cost of one vial of rFVIIa (Novoseven RT®) 1mg is more than $1,000, resulting in a total cost for the treatment of an average patient of approximately $7,000 to $12,000.

**rFVIIa for intracerebral haemorrhage**

The use of rFVIIa for intracerebral haemorrhage was declined for licensing in Australia. For this indication, the treatment group is poorly defined, optimal dosing strategy remains unclear and there is an uncertain risk:benefit ratio. For these reasons, **the use of rFVIIa for intracerebral haemorrhage is not supported unless further information becomes available.**
References


Biss TT, Hanley JP. Recombinant activated factor VII (rFVIIa/NovoSeven®) in intractable haemorrhage: use of a clinical scoring system to predict outcome. Vox Sanguinis 2006;90:45-52.


Recombinant activated factor VII (rFVIIa) (Eptacog Alfa)

Eligibility worksheet for major haemorrhage

Answers must be ‘yes’ to all inclusion criteria and ‘no’ to all exclusion criteria before use of rFVIIa can be considered. Medical superintendent or delegate authority should be obtained before administration.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>1. Ongoing life-threatening haemorrhage that surgical and mechanical efforts have failed to control</td>
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<tr>
<td>2. Eight or more units of packed red blood cells have been administered in the last six hours, along with coagulation factor replacement:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>a) 8 units FFP;</td>
<td></td>
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<td>b) 8 units platelets; and</td>
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<tr>
<td>c) If available, 10 units of cryoprecipitate (when fibrinogen is low)</td>
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<tr>
<td>3. Aggressive attempts to correct acidosis and hypothermia have been performed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4. Persisting coagulopathy despite appropriate factor and platelet replacement</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. When appropriate, specific pharmaceutical agents have been used for:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>a) Reversal of warfarin – vitamin K, prothrombin complex concentrate</td>
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<tr>
<td>b) Reversal of heparin – protamine sulfate</td>
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</tbody>
</table>

| Exclusions | Yes | No |
| 1. Severe acidosis < 7.05 | | |
| 2. Temperature < 34°C | | |
| 3. Gun shot wound to the head | | |

Treating specialist’s name: __________________________
Signature: __________________________ Date: __________________________

Medical superintendent or 2nd nominated specialist’s name: __________________________
Signature: __________________________ Date: __________________________

Dose: __________________________

Recommended dosing

For all scenarios, give an initial dose of 50 micrograms/kg. Clinical response is usually obvious within 30 minutes. If no response within 30 minutes, check for acidosis and hypothermia, and consider giving a repeat dose of rFVIIa (50 micrograms/kg). **Maximum of 2 doses to be used.** A total dose of > 100 micrograms/kg is unlikely to achieve additional haemostasis in major haemorrhage.

Use ideal body weight in patients > 100kg.
How to access rFVIIa vials
[Hospitals to indicate local procedure (including how to obtain stock after hours)].

Audit and follow-up
Worksheets must be completed and retained for future audit. Use should be reported to the local Drugs and Therapeutics Committee. Clinicians should also consider reporting of cases to the Haemostasis Registry once local Ethics Committee approval has been obtained. Hospitals should keep a local register, as this item will be subject to regular review by the Queensland Health Medicines Advisory Committee (QHMAC).

Follow up data:

Clinical condition: ________________________________

Estimated patient weight: ________________________________

Dose administered: ________________________________

Total blood products used prior to administration

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<thead>
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<tbody>
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<td>RBC</td>
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<td>Platelets</td>
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<td>Cryoprecipitate</td>
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Pathology

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<td>Platelets</td>
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Extra dose required: ________________

Patient outcome

Discharge from ICU—no. of days: ________________________________

Death—Cause of Death: ________________________________