Update on NovoSeven®
Contents

– What is NovoSeven?
– Current Indication
– How does NovoSeven work?
– Clinical settings under investigation
– Trauma Study
– ICH Study
– The Registry
What is NovoSeven?

- A recombinant coagulation factor
- Factor VIIa, eptacog alfa
- Is supplied as a white, lyophilised powder in single use glass vials.
- Each pack contains one vial
- Three presentations of NovoSeven:
  - 1.2mg / vial
  - 2.4mg / vial
  - 4.8mg / vial
In Australia and New Zealand NovoSeven is indicated for the control of bleeding and surgical prophylaxis in patients with inhibitors to coagulation factors VIII and IX.
How is NovoSeven produced?

Liver gene library → Human FVII gene

Amplification → Multiple copies of hFVII gene

Single copy of gene isolated → Incorporate into BHK cells

Expression of rFVII in culture medium

Activation and Purification → NovoSeven®

hFVII = human factor VII
BHK = baby hamster kidney
rFVIIa boosts thrombin generation on activated platelets
Clinical settings under investigation

Coagulation Disorders
- Factor VII deficiency
- Factor XI deficiency
- Von Willebrand Disease
- Glanzmann’s thrombasthenia
- Vitamin K antagonist therapy

Surgical Settings
- **Trauma**
  - Hepatectomy
  - Orthoptic liver transplant
  - Cardiac surgery
  - Spinal surgery
  - Pelvic reconstructive surgery

Other – Critical Bleeding
- Stem cell transplantation
- Dengue Fever
- Acute oesophageal varices
- **Intracerebral haemorrhage**
- Traumatic brain injury
- Post partum haemorrhage
- Burns
Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review

Figure 1. Published literature on recombinant factor VIIa until July 2004. The majority of publications regard case reports and case series (36% and 26%, respectively). There are 28 clinical trials (6%), 11 in hemophiliacs, three in patients (pts) with other coagulation defects, seven in patients with liver disease, one in surgical patients, and six concerning reversal of anticoagulation.
Concept and Product Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Activities/Events</th>
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<tr>
<td>1980-82</td>
<td>Basic research discovery of the role of Factor VIIa in coagulation initiation</td>
</tr>
<tr>
<td>1983</td>
<td>First successful treatment of haemophilia dogs with FVIIa</td>
</tr>
<tr>
<td>1983-88</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>1988</td>
<td>Treatment of first haemophilia patient with FVIIa</td>
</tr>
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<td>1988-92</td>
<td>Phase 1 and phase 2 trials with rFVIIa</td>
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<td>1992-96</td>
<td>Phase 2 and phase 3 trials in EU and US</td>
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<tr>
<td>1996</td>
<td>Registration in EU for treatment of haemophilia pts with inhibitors</td>
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<tr>
<td>1996-99</td>
<td>Phase 3 clinical trials in US</td>
</tr>
<tr>
<td>1999</td>
<td>Registration in US / 1st published use of NovoSeven® in trauma</td>
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<tr>
<td>2002</td>
<td>Registration in Japan</td>
</tr>
<tr>
<td>2004</td>
<td>New indications: FVII def. and Glanzmann’s disease</td>
</tr>
<tr>
<td>2004</td>
<td>Proof of concept: Trauma, ICH</td>
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Summary of current literature

Table 1

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<tr>
<th>Ref. (year)</th>
<th>Patients (n)</th>
<th>Type of study</th>
<th>Type of patients</th>
<th>Dose (μg/kg)</th>
<th>Reported reduction in transfusion requirements</th>
<th>Mortality (deaths; n)</th>
<th>Thrombotic complications</th>
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<td>[13] (1999)</td>
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<td>Case report</td>
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<td>6</td>
<td>1 DVT</td>
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<td>48–148</td>
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<td>Unpublished (2004)</td>
<td>277</td>
<td>Prospective phase II</td>
<td>Blunt and penetrating</td>
<td>200, 100, 100</td>
<td>Decreased</td>
<td>69</td>
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DVT, deep vein thrombosis; IAT, iliac artery thrombosis.
Phase 2 Trauma Trial


**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;59:8-18
Trauma Trial

Transfusion requirements & Volume replacement
ICU, hospital days
Survival
Adverse Events
MOF, ARDS, infections, SAE

**rFVIIa**

**Placebo**

| Time (h) | 0 - - - - - - 4 |
| Treatment | Max 12 hrs |
| Transfusion requirements & Volume replacement |
| ICU, hospital days |
| Survival |
| Adverse Events |
| MOF, ARDS, infections, SAE |

| 0 - 1 - 3 - 4 |
| 200, 100, 100 µg/kg bw |

rFVIIa
Placebo

Transfusion (units RBC)

0 6 8

Trauma Trial

Arrival ER Randomization

Transfusion

0 - - - - - - 4

To be published in journal of Trauma – end July 2005
rFVIIa significantly reduced the need for transfusion in BLUNT trauma

Percent of patients (%)

- Placebo (N=59)
- rFVIIa (N=52)

P = 0.019
Incidence of reported thrombo-embolic events with rFVIIa is similar to placebo

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<th>rFVIIa (N=70)</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
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<tr>
<td>Thrombo-embolic events</td>
<td>3</td>
<td>4.7</td>
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<tr>
<td>All adverse events</td>
<td>40</td>
<td>62.5</td>
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</table>
Australia and New Zealand Study - Trauma

A multi-center, randomized, double-blind, parallel group, placebo controlled trial to evaluate the efficacy and safety of activated recombinant factor VII in the treatment of refractory bleeding in severely injured trauma patients.

**Objectives**
To evaluate the efficacy and safety of rFVIIa as an adjunct to standard treatment of trauma patients with active hemorrhage refractory to treatment

**Trial population**
Randomized patients will receive the first dose of rFVIIa/placebo upon the start of the 4 units of RBC and no later than completion of the 8 units RBC. 1500 patients with receive placebo or rFVIIa. Dosed group will receive 200 µg/kg (0 hr), 100 µg/kg (1hr) and 100 µg/kg (3hr).

**Primary Endpoint**
**Efficacy**: 30 day mortality
**Safety**: Adverse events from administration of the initial dose of study drug through hour 48
Serious adverse events (SAEs) through Day 90

**Secondary Endpoints:**
**Efficacy**: at 15 minutes - clinical assessment of tissue bleeding on of each of the three doses of study drug
At 24 hrs - number of units of fresh frozen plasma (FFP), platelets and cryoprecipitate from the initial administration of study drug
At 48 hrs – mortality
Through day 30 – mortality, single organ failure for pulmonary, renal, cardiovascular and hepatic system, ventilator-free days, ICU- free days, hospital- free days
Through day 90 - mortality, ventilator-free days, ICU- free days, hospital- free days
**Safety**
DIC through day 5
Phase 2 ICH trial
Study design: global multi-center, randomised, double-blind, parallel group, placebo-controlled, dose response trial (F7-1371 ICH trial)

400 patients randomised

Baseline CT scan

- Placebo n = 100
- rFVIIa 40 µg/kg Single bolus injection n = 100
- rFVIIa 80 µg/kg Single bolus injection n = 100
- rFVIIa 160 µg/kg Single bolus injection n = 100

Primary end point:
Change in ICH volume

Secondary end points:
90 day outcome of relevant stroke scales

- Mortality
- mRS
- BI
- NIHSS
- eGOS
- GCS
- EuroQOL
- SAE

Timing of CT scanning: Baseline CT scan, 24 hrs post-dose, 72 hrs post-dose

Note: mRS: Modified Rankin Scale; BI: Barthel Index; NIHSS: National Institute of Health Stroke Scale; eGOS: Extended Glasgow Outcome Scale; GCS: Glasgow Coma Scale, EuroQOL: European Quality of life scale, SAE: Serious Adverse Events, including thrombo-embolic events
Modified Rankin Scale

SCORE DESCRIPTION

0  No symptoms at all

5  No significant disability despite symptoms; able to carry out all usual duties and activities

7  Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

9  Moderate disability; requiring some help, but able to walk without assistance

11 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

13 Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6  Dead
Modified Rankin Scale at Day 90 (disability)
**Australia Study - ICH**

A Randomised, Double-Blind, Placebo Controlled, Multi-Centre, Parallel Groups Confirmatory Efficacy and Safety Trial of Activated Recombinant Factor VII in Acute Intracerebral Haemorrhage

**Objectives**
To evaluate the efficacy and safety of recombinant activated factor VII in reducing disability and improving clinical outcome by preventing early haematoma growth in patients with acute intracerebral haemorrhage (ICH).

**Trial population**
A total of 600+ patients are randomised with three treatment arms: 20 µg/kg or 80 µg/kg rFVIIa or placebo

**Primary Endpoint**
**Efficacy:** modified Rankin Scale score (mRS) at Day 90.

**Secondary Endpoints**
**Efficacy:** absolute and percent change in ICH volume as measured by CT head scans from prior to dosing to 24 hours after the baseline scan
The Barthel Index (BI) at Day 15 and Day 90
Mortality

**Safety Endpoints:**
The occurrence of adverse events until hospital discharge or until Day 90, whichever comes first, and serious adverse events until the End of Trial Form is completed
Management of patients with Critical Bleeding and Coagulopathy

Appropriate Medical interventions
- prevent and reverse hypothermia
- prevent and reverse acidosis
- correct coagulopathy
- heparin reversal
- warfarin reversal
- consider antifibrinolytic agents

Laboratory Tests
Repeat blood tests after each 4-6 units RBCs
PT, APTT > 1.5 X control \(\rightarrow\) 4 units FFP
Fibrinogen < 1g/L \(\rightarrow\) 10 units cryoprecipitate
Platelet count < 75 X 10^9 \(\rightarrow\) 4 units of platelets
Consider calcium chloride

If bleeding and coagulopathy continue after conventional therapy
(usually: 10 units RBC, 8 units FFP, 8 units platelets, 10 units cryoprecipitate)
\textbf{10/8/8/10}

rFVIIa
100 µg/kg
(rounded to whole ampoule)

If no response in 20 minutes
Consider 2nd dose of rFVIIa
(100 µg/kg)

Note:
• Use of rFVIIa in children and pregnancy requires special consideration of risk/benefits
• Early use may be considered in high-risk groups e.g. patients with cirrhosis and undergoing liver surgery
Cardiac Cases
When is rFVIIa (NovoSeven) being used?

• Complex cases
• Prolonged Bypass
• Double Valve
• Deep Hypothermic Circulatory Arrest
• Elderly
• Endocarditis
How is rFVIIa (NovoSeven) being used in cardiac cases?

Two approaches:

• Out of theatre
  – Standard practice with haemostasis management
  – Back to ICU
  – >100 ml/hr → single dose of 60 - 90 ug/kg

• In theatre
  – Reversal of heparin
  – Management of surgical bleeders
  – Threshold of blood products (10,8,8,10)
  – Single dose - 90 ug/kg, trend to lower doses and repeat dosing
International Studies - Cardiac Study

A multi-centre, randomised, double-blind, placebo-controlled, dose escalation trial on safety and efficacy of activated recombinant factor VII in the treatment of post-operative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass.

Objectives
To evaluate safety and efficacy of recombinant activated factor VII (rFVIIa) in the treatment of postoperative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass.

Trial population
A total of 210 patients are dosed with 40, 80 and 160ug/kg BW. Each tier will contain 35 patients receiving active drug and 35 patients receiving placebo.

Duration of treatment
Single dose. All patients will be followed for 30 days after treatment (including trial visits during 5 days and a phone follow-up telephone call on day 30).

Methodology
Patients are randomised upon reaching a defined post-operative bleeding rate into chest drains to trial product or placebo. A mandatory transfusion protocol is followed thereafter to standardize haemostasis management. Transfusions of RBC, FFP and platelets are triggered based on bleeding rate and laboratory results of coagulation parameters.

End-points
Safety & Efficacy
Avoidance / reduction of allogenic transfusion after trial product administration. Health economics parameters e.g. days of ICU and ward hospitalization, time on ventilator.
Recombinant factor VIIa for life threatening post-partum haemorrhage

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<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Weeks of gestation</th>
<th>Type of delivery</th>
<th>Cause of bleeding</th>
<th>Interventions</th>
<th>No. of operations</th>
<th>Dose of rFVIIa (µg kg⁻¹)</th>
<th>Response to rFVIIa administration</th>
<th>Subsequent arterial embolization (+/-)</th>
<th>Bleeding before rFVIIa administration (litres)</th>
<th>Total bleeding (litres)</th>
<th>Haemoglobin* (g litre⁻¹)</th>
<th>Platelets† (10⁹ litre⁻¹)</th>
<th>P-TT‡ (%)</th>
<th>D-dimer§ (mg litre⁻¹)</th>
<th>RBC/FFP/platelets¶ (U)</th>
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</table>

Table 1 Characteristics of the 12 parturients with major PPH treated with rFVIIa and undergoing a subsequent selective arterial embolization. *Haemoglobin just before rFVIIa administration (normal range 117–155 g litre⁻¹); †platelets just before rFVIIa administration (normal range 150–360 g litre⁻¹); ‡P-TT just before rFVIIa administration (normal range 70–130%); §d-dimer, highest intraoperative value determined (normal value <0.5 mg litre⁻¹); ¶units of red blood cells, fresh frozen plasma and platelets transfused before and after rFVIIa administration.

VD, vaginal delivery; CS, Caesarean section; IVD, instrumental vaginal delivery; Lac, uterine, vaginal or other lacerations; PA, placenta accreta; AP, adherent placenta; At, atony; PP, placenta percreta; Hys, hysterectomy; Ut, uterotonies; P-TT, thromboplastin time; NA, not available.
## Cost effectiveness

<table>
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<td>60 ug/kg</td>
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<td>100 kg patient</td>
<td>~ $ 10,800</td>
<td>~ $ 7,200</td>
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<td>70 kg patient</td>
<td>~ $ 7,600</td>
<td>~ $ 5,000</td>
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Aims

**investigate** the safety, efficacy and dosing of rFVIIa in investigational use

**monitor** the extent, indications for, dosages and appropriateness of use

**generate** information to assess cost-effectiveness and to support clinical use

**publish** based on analyses of local experience

**provide** data for physicians, hospitals and Regulatory Authorities
‘State-us’ Report – Victoria/Tasmania

<table>
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<td>The Geelong Hospital</td>
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<td>The Austin</td>
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Ethics pending:

Royal Melbourne Hospital, Royal Children's Hospital, MMC, Dandenong, Knox Private, Peter McCallum, St Vincent’s, Royal Hobart
The Haemostasis Registry – Evidence and Practice

Louise E. Phillips¹, Peter A. Cameron¹,², John J. McNeil¹, James Isbister³

¹ Monash University Department of Epidemiology and Preventive Medicine ² Emergency and Trauma Centre, The Alfred
³ Royal North Shore Hospital, NSW

Introduction:
Recombinant activated factor VII (rFVIIa, marketed under the brand name NovoSeven®) is approved for the treatment of spontaneous and surgical bleeding in patients with haemophilia A or B and with antibodies to either factor VIII or factor IX. Recently rFVIIa has increasingly been used for indications outside the approved areas, particularly in cardiac surgery, trauma and other critical bleeding episodes. Use in these areas remains controversial.

Methods:
Monash University Department of Epidemiology and Preventive Medicine has established the Haemostasis Registry (with an unrestricted educational grant from Novo Nordisk Pharmaceuticals) to collect data on the use of rFVIIa, in patients with critical bleeding throughout Australia and New Zealand. Nineteen Hospitals have completed the process of joining the Haemostasis Registry, obtaining ethics approval and are awaiting ethics approval. A further 23 hospitals have agreed to participate in the Registry and are now able to submit data to the Registry. It is anticipated that all the major users of rFVIIa will contribute to the Registry. As at 15 November, we had received 168 cases. We hope to receive in excess of 300 cases by the end of 2005.

Results:
Preliminary data from the 168 cases received to date by the Haemostasis Registry are presented below. Cardiac Surgery is the main area of use in the hospitals reporting thus far. Refractory bleeding following other types of surgery, medical uses (such as for GI bleeding in patients with various forms of cancer) and trauma are also large areas of use. Most patients received a single dose of rFVIIa and, in the majority of cases, rFVIIa was administered relatively early in the course of patient bleeding (ie when 5 or fewer units of RBC had been used). Seventy percent of patients were male and approximately 70% of patients were 45 years of age or older. In 78% of cases the use of rFVIIa was considered to have had a positive effect on the control of bleeding. Six adverse events (3.57% of cases) were reported to be ‘probably’ or ‘possibly’ linked to the administration of rFVIIa. No adverse events were reported as being ‘definitely’ linked.

Conclusions:
Although randomized controlled trials are important in establishing the safety and efficacy of new treatments, they do not replace the need for registries, especially for treatments where clinicians believe that withholding treatment may be unethical because of potential life threatening consequences. This problem is made more difficult where there are a wide range of applications. As more data becomes available, the Haemostasis Registry data will help to elucidate the safety and efficacy of rFVIIa and provide important feedback to doctors and hospitals.
Registry cases to 15 November 2005
n=168
### Average Dose of rFVIIa

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of doses</th>
<th>Average Dose (mg)</th>
<th>Average Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>168</td>
<td>207</td>
<td>6.53</td>
<td>0.084</td>
</tr>
</tbody>
</table>
Effect of rFVIIa on Bleeding
Number of doses of rFVIIa
RBC use before rFVIIA usage
## Adverse Events

<table>
<thead>
<tr>
<th>Type of Adverse Event</th>
<th>Linked to rFVIIa?</th>
<th>No.</th>
<th>Details of Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic</td>
<td>Probably</td>
<td>2</td>
<td>1. Small clot around aortic graft. 2. Clots formed in chest drain following cardiac surgery.</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>Possibly</td>
<td>3</td>
<td>1. CVA 2. CVA 3. Intracardiac thrombus</td>
</tr>
<tr>
<td>Allergic</td>
<td>Possibly</td>
<td>1</td>
<td>1. Rash on trunk.</td>
</tr>
</tbody>
</table>