NovoSeven® RT (Coagulation Factor VIIa [Recombinant])

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use NovoSeven® RT safely and effectively. See full prescribing information for complete boxed warning.

- **Indications** and Usage,
- **Warnings** and Precautions (5.1, 5.2)

**Recent Major Changes**

**Boxed Warning**: 07/2014

**Indications and Usage**: 07/2014

**Dosage and Administration**: 04/2014

**Warnings and Precautions**: 07/2014

**Recent MAJOR CHANGES**

NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for:
- Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann’s thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets (1)
- Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia (1)

**DOSE AND ADMINISTRATION**

For intravenous bolus injection only
- Administer NovoSeven® RT to patients only under the supervision of a physician experienced in the treatment of bleeding disorders (2.1)
- After reconstitution, administer within 3 hours; do not freeze or store in syringes (2.3)

### Bleeding Episodes (2.1)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Congenital Hemophilia A or B with Inhibitors</td>
<td>• 90 mcg/kg every 2 hours, repeat every 2 hours during surgery.</td>
</tr>
<tr>
<td>Acquired Hemophilia</td>
<td>• 70-90 mcg/kg every 2-3 hours until hemostasis is achieved.</td>
</tr>
<tr>
<td>Congenital Factor VII Deficiency</td>
<td>• 15-30 mcg/kg every 4-6 hours until hemostasis is achieved.</td>
</tr>
<tr>
<td>Glanzmann’s Thrombasthenia</td>
<td>• 90 mcg/kg every 2-6 hours until hemostasis is achieved.</td>
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</table>

### Peri-operative Management (2.1)

<table>
<thead>
<tr>
<th>Indication</th>
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<tbody>
<tr>
<td>Congenital Hemophilia A or B with Inhibitors</td>
<td>Minor: 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery.</td>
</tr>
<tr>
<td>Acquired Hemophilia</td>
<td>70-90 mcg/kg immediately before surgery, repeat every 2-3 hours for the duration of surgery and until healing has occurred.</td>
</tr>
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<td>15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of surgery and until hemostasis is achieved.</td>
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<tr>
<td>Glanzmann’s Thrombasthenia</td>
<td>90 mcg/kg immediately before surgery and every 2 hours for the duration of the procedure.</td>
</tr>
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</table>

**ADVERSE REACTIONS**

The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-668-6777 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Avoid simultaneous use of NovoSeven® RT and aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) (7)
- Do not mix with other infusion solutions (7)
- Do not administer NovoSeven® RT with coagulation factor XIII (FXIII) (7)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: No human or animal data. Use only if clearly needed. (8.1)
- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 07/2014

**REFERENCES**

- Pharmacodynamics
- Pharmacokinetics
- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology and/or Pharmacology
- CLINICAL STUDIES
- Hemophilia A or B with Inhibitors
- Congenital Factor VII Deficiency
- Acquired Hemophilia
- Glanzmann’s Thrombasthenia

**NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

**FULL PRESCRIBING INFORMATION: CONTENTS**

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2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
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   8.5 Geriatric Use
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10 DESCRIPTION
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   12.1 Mechanism of Action
12 13 14 15 16 17

*Sections or subsections omitted from the full prescribing information are not listed.*
**INDICATIONS AND USAGE**

NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for:

- Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann’s thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia

2 **DOSAGE AND ADMINISTRATION**

For intravenous bolus administration only

2.1 **Dose**

- Initiate treatment with NovoSeven® RT under the supervision of a qualified healthcare professional experienced in the treatment of bleeding disorders.
- Use hemostasis evaluation to determine the effectiveness of NovoSeven® RT and to provide a basis for modification of the NovoSeven® RT treatment schedule.
- Coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven® RT.

Table 1: Dosing for Treatment of Acute Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Dose and Frequency</th>
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<td>Congenital Hemophilia A or B with Inhibitors</td>
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<tr>
<td>Hemostatic</td>
<td>90 mcg/kg every 2 hours, adjustable based on severity of bleeding</td>
<td>Until hemostasis is achieved, or until the treatment has been judged to be inadequate</td>
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<td>Post-Hemostatic</td>
<td>90 mcg/kg every 3-6 hours for severe bleeds</td>
<td>After hemostasis is achieved to maintain the hemostatic plug</td>
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**Perioperative Management**

NovoSeven® RT dosing for prevention of bleeding in surgical interventions or invasive procedures (perioperative management) is provided in Table 2.

Table 2: Dosing for Perioperative Management

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**Glanzmann’s Thrombasthenia**

90 mcg/kg every 2-6 hours in severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved

Platelet transfusions are the primary treatment in patients with Glanzmann's Thrombasthenia without refractoriness to platelets or in patients without platelet-specific antibodies

- For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds. A majority of patients who reported adverse experiences received more than twelve doses. Monitor and minimize the duration of any post-hemostatic dosing.

Perioperative Management

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**Reconstitution**

- Follow the procedures below for the preparation and reconstitution of NovoSeven® RT. For questions regarding reconstitution, please contact Novo Nordisk at 1-877-NOVO-777.
- Calculate the NovoSeven® RT dosage and select the appropriate NovoSeven® RT package provided with either 1 histidine diluent vial or 1 pre-filled histidine diluent syringe.

- Reconstitute only with the histidine diluent provided with NovoSeven® RT.

**Diluent vial**

- Plastic cap
- Rubber stopper
- Histidine diluent

**Powder vial**

- Plastic cap
- Rubber stopper
- Vial adapter
- Spike (under protective paper)
- Plunger rod
- Pre-filled syringe with diluent
- Syringe tip (under syringe cap)
- Protective paper
- Scale

1. Always use aseptic technique.
2. Bring NovoSeven® RT (white, lyophilized powder) and the specified volume of histidine (diluent) to room temperature, but not above 37°C (98.6°F). The specified volume of diluent corresponding to the amount of NovoSeven® RT is as follows: 1 mg (1000 micrograms) vial = 1 mL Histidine diluent
3. Remove vials of NovoSeven® RT from the refrigerated condition 2 hours prior to use.

**WARNING: THROMBOSIS**

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported.
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT.
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. [See Warnings and Precautions (5.1)]

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- The minimum effective dose has not been determined.

**2.2 Reconstitution**

- Follow the procedures below for the preparation and reconstitution of NovoSeven® RT. For questions regarding reconstitution, please contact Novo Nordisk at 1-877-NOVO-777.
- Calculate the NovoSeven® RT dosage and select the appropriate NovoSeven® RT package provided with either 1 histidine diluent vial or 1 pre-filled histidine diluent syringe.

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<td>Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery Post surgical: 90 mcg/kg every 2 hours to prevent post-operative bleeding*</td>
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*The minimum effective dose has not been determined.
2. Administration

For intravenous bolus injection only

1. Use aseptic technique.
2. Draw back the plunger of a sterile syringe (attached to sterile needle) and add the solution.
3. Insert needle into the vial of reconstituted NovoSeven® RT and inject the air into the vial and then withdraw the appropriate amount of reconstituted NovoSeven® RT into the syringe.
4. Remove and discard the needle from the syringe.

NovoSeven® RT package containing 1 vial of NovoSeven® RT powder and 1 vial of histidine diluent with vial adapter for needleless reconstitution:

1. Always use aseptic technique.
2. Invert the NovoSeven® RT vial. Stop pushing the plunger rod and let it move back on its own while the solution fills the syringe.
3. Unscrm the vial adapter with the vial. Discard the empty NovoSeven® RT vial with the vial adapter attached.

Caution:

- The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector.
- Needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave®, MicroClave®, Invision-Plus®, Invision-Plus CS®, Invision-Plus® Junior®, Biojector®), and their use can damage the connector and affect administration. To administer product through incompatible needleless connectors, withdraw reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe.
- If you have encountered any problems with attaching the pre-filled histidine diluent syringe to any Luer-lock compatible device, please contact Novo Nordisk (at 877-666-6777).

Administer NovoSeven® RT using the following procedures:

1. Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose.
2. If line needs to be flushed before or after NovoSeven® RT administration, use 0.9% Sodium Chloride Injection, USP.
3. Discard any unused reconstituted NovoSeven® RT after 3 hours.

3. Dosage Forms and Strengths

NovoSeven® RT is available as a white lyophilized powder in single-use vials containing 1 mg (1000 micrograms), 2 mg (2000 micrograms), 5 mg (5000 micrograms), or 8 mg (8000 micrograms) reconstituent coagulation Factor VIIa (FVIIa) per vial.

The diluent for reconstitution of NovoSeven® RT is a 10 mmol solution of L-histidine in water for injection. It is a clear colorless solution provided in a vial or a pre-filled diluent syringe and is referred to as the histidine diluent.

After reconstitution with the histidine diluent, the final solution contains approximately 1 mg per mL NovoSeven® RT (1000 micrograms per mL).

5. Contraindications

None known.

6. Adverse Reactions

The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice.

Adverse reactions outlined below have been reported from clinical trials and data collected in registries.

Hemophilia A or B Patients with Inhibitors

In two studies for hemophilia A or B patients with inhibitors treated for bleeding episodes (N=298), adverse reactions were reported in 22% of the patients that were treated with NovoSeven® for 1,939 bleeding episodes (see Table 3 below).

Table 3: Adverse Reactions Reported In ≥2% of the 298 Patients with Hemophilia A or B with Inhibitors

<table>
<thead>
<tr>
<th>Body System</th>
<th># of adverse reactions (n=1,939 treatments)</th>
<th># of patients (n=298 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>Fever</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Platelets, Bleeding, and Clotting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrinogen decreased</td>
<td>10</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
<td>9</td>
</tr>
</tbody>
</table>

Serious adverse reactions included thrombosis, pain, thrombophilic bits deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, anemia pectoris, DIC, anaphylactic shock and shock-like reaction, and dysfunction.

The most common adverse reactions of DIC and therapeutic response decreased had a fatal outcome.

There have been no confirmed reports of inhibitory antibodies against NovoSeven® or FVII in patients with congenital hemophilia A or B.

In two clinical trials evaluating safety and efficacy of NovoSeven® administration in the peri-operative setting in hemophilia A or B patients with inhibitors (N=51), the following serious adverse reactions were reported: acute post-operative hemorrhage (n=1), intraluminal jugular thrombosis adverse reaction (n=1), decreased therapeutic response (n=1).

Congenital Factor VII Deficiency

Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetic study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that 75 patients with Factor VII deficiency had received NovoSeven® to patients for 124 bleeding episodes, surgeries, and prophylactic; 5 patients in the pharmacokinetics trial. The following adverse reactions were reported: intracranial hypertension (n=1), IgG antibody against FVIIa and FVIII (n=1), localized phlebitis (n=1).

As with all therapeutic proteins, there is a potential for the potential for immunogenicity. Patients with factor VII deficiency treated with NovoSeven® RT were found to be factor VII antibodies.

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patients experienced 8 serious adverse reactions. Serious adverse reactions included shock (n=1), cerebrovascular accident (n=1), acute thrombocytopenic events (n=6) which included intracerebral hemorrhage, occlusion, cerebral ischemia, angina pectoris, myocardiac infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions had a fatal outcome.

Glanzmann’s Thrombasthenia

Data collected from the Glanzmann’s Thrombasthenia Registry (GTR) and the HTRS registry showed that 140 patients with Glanzmann’s thrombasthenia received NovoSeven® RT for 518 bleeding episodes, surgeries or traumatic injuries. The following adverse reactions were reported: deep vein thrombosis (n=1), headache (n=2), fever (n=2), nausea (n=1), and dyspnea (n=1).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of NovoSeven®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Table 4: Post Marketing Experience

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including anaphylactic shock, flushing, urticaria, rash, angioedema)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic events (including hepatic artery thrombosis, myocardiach infarction, cerebral infarction, intestinal infarction, intracardiac thrombus, peripheral ischemia, cerebral vein thrombosis, myocardiach ischemia, renal artery thrombosis)</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

• Avoid simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates. The risk of a potential interaction between NovoSeven® RT and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies.

• Do not mix NovoSeven® RT with infusion solutions.

Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII. (See Nonclinical Toxicology (13.2))

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NovoSeven® RT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Treatment of rats and rabbits with NovoSeven® in reproduction studies has been associated with mortality at doses up to 6 mg/kg body weight and 5 mg/kg body weight respectively. At 6 mg/kg body weight in rats, the abortion rate was 0 out of 25 litters; at 12 mg/kg body weight and 5 mg/kg body weight respectively. At 6 mg/kg body weight in rabbits, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg/kg body weight of NovoSeven® gave birth successfully, however, two of the 23 litters died during the early part of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven®.

8.2 Labor and Delivery

There are no adequate and well-controlled studies in labor, delivery, and postpartum periods. NovoSeven® RT has caused thrombosis when used to control post-partum hemorrhage.

8.3 Nursing Mothers

It is unknown whether NovoSeven® RT is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age. The safety and effectiveness of NovoSeven® RT has not been studied to determine if there are differences among various age groups, from infants to adolescents (0 to 16 years of age).

In the Glanzmann’s Thrombasthenia Registry, NovoSeven® was used in 43 children aged 0-12 years for 157 bleeding episodes and in 15 children aged 0-12 years for 19 surgical procedures. NovoSeven® also was used in 8 children aged >12 to 16 years for 8 surgical procedures. Efficacy of regimens including NovoSeven® also was used in 8 children aged >12 to 16 years for 8 surgical procedures. In this model, fresh human blood was treated with corn trypsin inhibitor (CTI) to block the contact pathway of blood coagulation. Tissue factor (TF) was added to initiate clotting in the presence and absence of rFVIIa for both types of blood. In a separate model, and in line with previous reports, escalating doses of rFVIIa in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/mL. Coagulation initiated by addition of tissue factor and CaCl2. Thrombin generation was measured in the presence of a thrombin substrate and various added concentrations of rFVIIa.

Figure A

TF-initiated clotting of normal blood and congenital hemophilia A blood in the presence of factor VIIa.

Figure B

TF-initiated clotting of normal blood and congenital hemophilia A platelet rich plasma in the presence of rFVIIa.
micrograms per kg body weight, showed no significant difference between the two doses used with regard to dose-independent parameters. Mean results for the two doses (15, 30) are shown in Table 5. Incremental recovery was 18.3% (0.44 U/dl/kg) and 22.2% (0.51 U/dl/kg) for the 15 and 30 mcg/kg NovoSeven® RT doses, respectively. No adverse reactions were reported in the pharmacokinetic study.

The normal Factor VII plasma concentration is 0.5 micrograms per mL. Factor VII levels of 15-25% (0.075 – 0.125 micrograms per mL) are generally sufficient to achieve normal hemostasis. For example, a 70 kg individual with FVII deficiency (plasma volume of approximately 3000 mL) would thus require 3.2 – 5.4 micrograms per kg of NovoSeven® RT to secure hemostasis, assuming 100% recovery but, in many patients, recovery rates vary. For FVII deficient patients, a NovoSeven® RT dose range of 10-20 micrograms per kg would be required to achieve sufficient FVIII plasma levels for hemostasis, which is consistent with the recommended dose range.

Table 5: Single Dose Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Formulation (n)</th>
<th>rFVIIa (n=35)</th>
<th>rFVIIa (n=22)*</th>
<th>rFVIIa-25C (n=22)*</th>
<th>rFVIIa (n=15)</th>
<th>rFVIIa (n=5)</th>
<th>FVIII Deficiency†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages</td>
<td>20-45</td>
<td>22-44</td>
<td>15-30</td>
<td>53-60</td>
<td>2-20</td>
<td></td>
</tr>
<tr>
<td>Doses (mcg/kg)</td>
<td>40, 80, 160</td>
<td>90</td>
<td>175, 70, 35</td>
<td>90, 190, 150</td>
<td>15, 30</td>
<td></td>
</tr>
<tr>
<td>CL (mL/kg)</td>
<td>33 - 37</td>
<td>37.63</td>
<td>40.43</td>
<td>31.00</td>
<td>39, 58</td>
<td></td>
</tr>
<tr>
<td>τ (h)</td>
<td>3.9 - 6.0</td>
<td>3.48</td>
<td>3.54</td>
<td>2.89</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>130 - 165</td>
<td>111.31</td>
<td>122.96</td>
<td>106.5</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>2.7</td>
<td>3.07</td>
<td>3.4</td>
<td>3.4</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

*Based upon the 90 mcg/kg dose
AUC Area under the curve, CI, Clearance, τ, τ/2 terminal half-life, Vss Volume of distribution at steady state, MRT mean residence time, ND not determined, rFVIIa (NovoSeven® original formulation), rFVIIa-25C (NovoSeven® RT)

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Two mutagenicity studies have given no indication of carcinogenic potential for NovoSeven®. The clastogenic activity of NovoSeven® was tested in vitro and in vivo studies (i.e. bone marrow and in vivo studies (i.e. mouse micronucleus test). Neither of these studies indicated clastogenic activity for NovoSeven®. Other gene mutation studies have not been performed with NovoSeven® RT (e.g., Ames test). No chronic carcinogenic studies have been performed with NovoSeven® RT.

A reproductive study in male and female rats at dose levels up to 3.0 mg/kg per kg per day had no effect on mating performance, fertility, or litter characteristics. Treatment of rats and rabbits with NovoSeven® in reproductive studies has been associated with a mortality at doses up to 10 mg/kg and 5 mg/kg. At 6 mg/kg in rats, the abortion rate was 2 out of 25 litters; in rabbits at 5 mg/kg, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg/kg per kg of NovoSeven® gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven®.

13.2 Animal Toxicology and/or Pharmacology
In a monkey cardiovascular safety pharmacology model evaluating the effect of NovoSeven® (35 micrograms per kg) on cardiac electrical function, the Factor XIII A-Subunit (Recombinant) (85 I.U./kg, 17 times the expected human dose) in combination with rFVIIa (1000 mcg/kg, 11 times the expected human dose), one of the twelve monkeys died 4 hours after treatment due to thrombosis. Procoagulant risk factors, including indwelling catheters per monkey and the induction of anesthesia, may have complicated the study results. It is unclear whether the mortality was related to the overdose of one or both products, or a specific interaction between them. Nonclinical and clinical studies with the combination of rFVIIa and NovoSeven® RT at recommended human doses have not been performed.

14 CLINICAL STUDIES
14.1 Hemophilia A or B with Inhibitors
The largest number of patients (N=483) who received NovoSeven® in the United States were in the Factor VIII Deficiency (range) 14.2 Congenital Factor VII Deficiency

Data were collected from the published literature, compassionate use trials and registries for 70 patients with Factor VII deficiency treated with NovoSeven® for 124 bleeding episodes, surgeries, or prophylaxis regimens. Thirty-two of these patients were enrolled in emergency and compassionate use trials conducted by Novo Nordisk (43 non-surgical bleeding episodes, 26 surgeries), 35 were reported in the published literature (20 surgeries, 10 non-surgical bleeding episodes, 4 cases of caesarean section or vaginal birth, and 10 cases of long-term prophylaxis, and 1 case of on-demand therapy), and 3 patients were in the registry maintained by the Hemophilia and Thrombosis Research Society (9 bleeding episodes, 1 surgery).

Dosing ranged from 6 to 96 micrograms per kg administered every 2-12 hours (except for prophylaxis, where doses were administered from 2 times per day up to 2 times per week). Patients were treated with an average of 1-10 doses. Treatment was effective (bleeding stopped or treatment was rated as effective by the physician) in 93% of episodes (90% for trial patients, 98% for published patients, 90% for HTRS registry patients).

14.3 Acquired Hemophilia
Data were collected from four studies in a compassionate use program conducted by Novo Nordisk and the Hemophilia and Thrombosis Research Society (HTRS). The studies were not designed to select doses or compare first-line efficacy or efficacy when used after failure of other hemostatic agents (salvage treatment). A total of 70 patients with acquired hemophilia were treated with NovoSeven® for 113 bleeding episodes, surgeries, or traumatic injuries. Thirty-one of these patients were from the compassionate use program with 100 bleeding episodes (68 non-surgical and 32 surgical bleeding episodes) and 9 patients were from the HTRS registry with 13 bleeding episodes (8 non-surgical, 3 surgical and 2 traumatic injuries). Overall efficacy for the first-line treatment was 38/44 (86%) compared to 39/56 (70%) when used as salvage treatment (Table 8).

Table 7: Dosing by Treatment Group

<table>
<thead>
<tr>
<th>Bolus Injection 30 micrograms/kg</th>
<th>Continuous Infusion 50 micrograms/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of dosing, median (range)</td>
<td>10-4 (15)*</td>
</tr>
<tr>
<td>No. bolus injections, median (range)</td>
<td>38 (36-42)</td>
</tr>
<tr>
<td>Outcome (n)</td>
<td>Unknown 61 64-79 80-91 92-95 Total</td>
</tr>
<tr>
<td>Effective (%)</td>
<td>3 (3) 3 (5) 5 (6) 10 (9) 15 (12) 36 (57) 68 (57) 100</td>
</tr>
<tr>
<td>Partial (%)</td>
<td>3 (3) 0 (0) 0 (0) 3 (1) 3 (1) 4 (6) 21 (14) 20 (29) 20</td>
</tr>
<tr>
<td>Ineffective (%)</td>
<td>0 (0) 1 (2) 5 (6) 7 (10) 2 (3) 3 (10) 1 (6) 17 (16) 17</td>
</tr>
<tr>
<td>Treatment groups</td>
<td>NovoSeven® 50 micrograms/kg/h</td>
</tr>
</tbody>
</table>

* Includes one patient with acquired hemophilia
† Includes dosing during the follow-up period after the 10-day study period.

Table 8: Efficacy by Dose Group, for Patients Receiving Doses Ranging from <61 to >90 micrograms/kg NovoSeven®, Compassionate Use Programs and HTRS Registry

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unknown</th>
<th>&lt;61</th>
<th>61-69</th>
<th>70-80</th>
<th>81-91</th>
<th>92-95</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective (%)</td>
<td>3 (3) 3 (5) 5 (6) 10 (9) 15 (12) 36 (57) 68 (57) 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial (%)</td>
<td>3 (3) 0 (0) 0 (0) 3 (1) 3 (1) 4 (6) 21 (14) 20 (29) 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ineffective (%)</td>
<td>0 (0) 1 (2) 5 (6) 7 (10) 2 (3) 3 (10) 1 (6) 17 (16) 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Bleeding Episodes</td>
<td>3 4 8 16 21 15 45 112</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Outcome assessed at end of treatment, last observation carried forward
† One patient in the HTRS registry was excluded from efficacy analysis since NovoSeven® was used to maintain hemostasis before bleeding had been controlled.
‡ N (%) not add up to 100 due to rounding.
Overall, treatment with NovoSeven® RT was successful in 94.4% of bleeding episodes (Table 9) and 99.4% of surgical procedures (Table 13) with 143/160 (83.8%) and major (26/160, 16.3%) procedures. Dental procedures were most common (106, 66.3%), followed by endoscopy (100, 61.9%). Surgical procedures treated with NovoSeven® RT included minor (35, 21.1%), major (26, 16.3%) procedures. In HTRS, there were 7 patients that were treated with NovoSeven® RT, Coagulation Factor VIIa (Recombinant), 7% of the bleeding episodes were in pediatric patients (65%; children and adolescents, 0-16 yrs.).

Table 9: Adjuvant Evaluation of Efficacy – Bleeding Episodes for GTR Data

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>No. of patients</th>
<th>No. of episodes</th>
<th>Success</th>
<th>Failure</th>
<th>Insufficient data</th>
<th>No Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>NovoSeven® only</td>
<td>44</td>
<td>109</td>
<td>101 (92.7)</td>
<td>2 (1.8)</td>
<td>4 (3.7)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>NovoSeven® ± Platelets ± Other hemostatic agents</td>
<td>69</td>
<td>157</td>
<td>150 (95.5)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>By Antibody/Refactory Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractoriness ± Platelet-specific antibodies</td>
<td>31</td>
<td>79</td>
<td>75 (94.9)</td>
<td>2 (2.5)</td>
<td>2 (2.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Platelet-specific antibodies</td>
<td>8</td>
<td>10</td>
<td>10 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Neither or unknown</td>
<td>57</td>
<td>177</td>
<td>166 (93.8)</td>
<td>2 (1.1)</td>
<td>4 (2.3)</td>
<td>5 (2.8)</td>
</tr>
</tbody>
</table>

* All treatment regimens that included treatment with NovoSeven®
   a Includes GPIb/IIa, HLA, and unspecified platelet-specific antibodies
   b Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown
   c Patient numbers are not additive. Patients may have different episodes with treatment regimens and have more than one antibody/refractory status
   d Treatment was NovoSeven® only for 26/79 episodes with refractoriness with or without antibodies. 2/10 episodes with platelet specific antibodies only, and 81/177 episodes with neither or unknown. The remainder received NovoSeven® with platelets and/or antifibrinolytic agents.

Table 10: Adjuvant Evaluation of Efficacy – Surgical Procedures for GTR Data

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>No. of patients</th>
<th>No. of procedures</th>
<th>Success</th>
<th>Insufficient data</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NovoSeven®</td>
<td>77</td>
<td>160</td>
<td>159 (99.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>NovoSeven® only</td>
<td>35</td>
<td>66</td>
<td>65 (98.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>NovoSeven® ± Platelets ± Other hemostatic agents</td>
<td>57</td>
<td>94</td>
<td>94 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>By Antibody/Refactory Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractoriness ± Platelet-specific antibodies</td>
<td>33</td>
<td>70</td>
<td>69 (98.6)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Platelet-specific antibodies</td>
<td>11</td>
<td>24</td>
<td>24 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Neither or unknown</td>
<td>36</td>
<td>66</td>
<td>66 (100.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

* All treatment regimens that included treatment with NovoSeven®
   a Includes GPIb/IIa, HLA, and unspecified platelet-specific antibodies
   b Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown
   c Patient numbers are not additive. Patients may have different episodes with treatment regimens and have more than one antibody/refractory status
   d No reports of failure or lack of consensus was reported
   e Treatment was NovoSeven® only for 22/70 episodes with refractoriness with or without antibodies, 13/24 episodes with platelet specific antibodies only, and 31/86 episodes with neither or unknown. The remainder received NovoSeven® with platelets and/or antifibrinolytic agents.

**REFERENCES**


**16 HOW SUPPLIED/STORAGE AND HANDLING**

How Supplied NovoSeven® RT, Coagulation Factor VIIa (Recombinant), is supplied as a room temperature stable, white, lyophilized powder in single-use vials in cartons. The diluent for reconstitution for NovoSeven® RT is a 10 mmol solution of L-histidine in water for injection and is supplied as a clear colorless solution, and referred to as the histidine diluent. The histidine diluent is provided in either a vial or pre-filled diluent syringe. The amount of rFVIIa in milligrams and in micrograms is stated on the label.

NovoSeven® RT package containing 1 vial of NovoSeven® RT powder and 1 vial of histidine diluent:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg per vial (1000 micrograms/vial)</td>
<td>NDC 0169 7010 01</td>
<td>NovoSeven® RT in a single-use vial</td>
</tr>
<tr>
<td>2 mg per vial (2000 micrograms/vial)</td>
<td>NDC 0169 7020 01</td>
<td>NovoSeven® RT in a single-use vial</td>
</tr>
<tr>
<td>5 mg per vial (5000 micrograms/vial)</td>
<td>NDC 0169 7050 01</td>
<td>NovoSeven® RT in a single-use vial</td>
</tr>
<tr>
<td>8 mg per vial (8000 micrograms/vial)</td>
<td>NDC 0169 7040 01</td>
<td>NovoSeven® RT in a single-use vial</td>
</tr>
</tbody>
</table>
NovoSeven® RT with MixPro® package containing 1 vial of NovoSeven® RT powder and 1 pre-filled histidine diluent syringe with sterile vial adapter which serves as an alternative needleless reconstitution system:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
</table>
| 1 mg per vial (1000 micrograms/vial) | NDC 0169 7201 01 | • NovoSeven® RT in a single-use vial [NDC 0169-7211-11]  
  • Pre-filled histidine diluent in syringe, 1 mL [NDC 0169-7011-98]  
  • Vial adapter |
| 2 mg per vial (2000 micrograms/vial) | NDC 0169 7202 01 | • NovoSeven® RT in a single-use vial [NDC 0169-7212-11]  
  • Pre-filled histidine diluent in syringe, 2 mL [NDC 0169-7012-98]  
  • Vial adapter |
| 5 mg per vial (5000 micrograms/vial) | NDC 0169 7205 01 | • NovoSeven® RT in a single-use vial [NDC 0169-7215-11]  
  • Pre-filled histidine diluent in syringe, 5 mL [NDC 0169-7015-98]  
  • Vial adapter |
| 8 mg per vial (8000 micrograms/vial) | NDC 0169 7208 01 | • NovoSeven® RT in a single-use vial [NDC 0169-7218-11]  
  • Pre-filled histidine diluent in syringe, 8 mL [NDC 0169-7018-98]  
  • Vial adapter |

The NovoSeven® RT and histidine diluent vials are made of glass closed with a chlorobutyl rubber stopper not made with natural rubber latex, and covered with an aluminum cap. The pre-filled diluent syringes are made of glass, with a siliconised bromobutyl rubber plunger not made with natural rubber latex. The closed vials and pre-filled diluent syringes are equipped with a tamper-evident snap-off cap which is made of polypropylene. A vial adapter with 25 micrometer filter is provided with the pre-filled diluent syringe.

Storage and Handling
Prior to reconstitution, store NovoSeven® RT powder and histidine diluent between 2–25°C (36–77°F). Do not freeze. Store protected from light. Do not use past the expiration date.

After reconstitution, store NovoSeven® RT either at room temperature or refrigerated for up to 3 hours. Do not freeze reconstituted NovoSeven® RT or store in syringes.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Instructions for Use)
• Inform patients receiving NovoSeven® RT the benefits and risks associated with treatment.
• Advise patients about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
• Advise patients about the signs of thrombosis, including new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech.
• Advise patients to immediately seek medical help if any of the above signs or symptoms occur.

Version: 20140702-V13
NovoSeven® RT is covered by US Patent No. 8,299,029, and other patents pending.
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NovoSeven® is a registered trademark of Novo Nordisk Health Care AG.
Clave® and MicroClave® are registered trademarks of ICU Medical Inc.
MixPro® is a registered trademark of Novo Nordisk A/S.
InVision-Plus®, InVision-Plus CS®, InVision-Plus® Junior® are registered trademarks of RyMed Technologies, Inc.
Bionector® is a registered trademark of Vygon.
For information contact:
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600 Scudders Mill Road
Plainsboro, NJ 08536, USA
1-877-NOVO-777
www.NovoSevenRT.com
Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark
License Number: 1261
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Instructions for Use

Read these instructions carefully before using NovoSeven® RT.

1. Prepare the vial and the syringe
   - Take out the number of NovoSeven® RT packages you need.
   - Check the expiration date.
   - Check the name and the color of the package, to make sure it contains the correct product.
   - Wash your hands and dry them properly using a clean towel or air dry.
   - Take the vial, the vial adapter and the pre-filled syringe out of the carton. Leave the plunger rod untouched in the carton.
   - Bring the vial and the pre-filled syringe to room temperature (not above 98.6°F (37°C)). You can do this by holding them in your hands until they feel as warm as your hands.
   - Remove the plastic cap from the vial. If the plastic cap is loose or missing, don’t use the vial.
   - Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to dry for a few seconds before use. Don’t touch the rubber stopper after wiping it.

2. Attach the vial adapter
   - Remove the protective paper from the vial adapter.
   - Don’t touch the vial adapter out of the protective cap.
   - If the protective paper is not fully sealed or if it is broken, don’t use the vial adapter.

3. Attach the plunger rod and the syringe
   - Grasp the plunger rod by the wide top end and take it out of the carton. Be careful not to touch the sides or the thread of the plunger rod.
   - Keep holding the plunger rod at the wide top end.
   - Immediately connect the plunger rod to the syringe by turning it clockwise into the rubber plunger inside the pre-filled syringe until resistance is felt.
   - Remove the syringe cap from the pre-filled syringe by bending it down until the perforation breaks.
   - Don’t touch the syringe tip under any circumstances. If the syringe cap is loose or missing, don’t use the pre-filled syringe.

4. Mix the powder with the diluent
   - Hold the pre-filled syringe slightly tilted with the vial pointing downwards.
   - Push the plunger rod to inject all the diluent into the vial.

5. Inject the mixed solution
   - NovoSeven® RT is now ready to inject into your vein.
   - Do not mix NovoSeven® RT with any other intravenous infusions or medications.
   - Inject the mixed solution slowly over 2 to 5 minutes as instructed by your doctor or nurse.
   - Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or subcutaneous port.
   - Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and central venous access device in consultation with your doctor or nurse.
   - Injecting into a CVAD may require using a sterile 10 ml plastic syringe for withdrawal of the mixed solution and injection.
   - If necessary, use 0.9% Sodium Chloride Injection, USP to flush the CVAD line before or after NovoSeven® RT injection.

Disposal

- After injection, safely dispose of the syringe with the infusion set, the vial with the vial adapter, any unused NovoSeven® RT and other waste materials as instructed by your doctor or nurse.
- Don’t throw it out with the ordinary household trash.

Don’t disassemble the vial and vial adapter before disposal.
Don’t reuse the equipment.

NovoSeven® RT is recommended to be used immediately after it is mixed.
If you cannot use the mixed NovoSeven® RT solution immediately, it can be kept in the vial, still with the vial adapter and the syringe attached, at room temperature or refrigerated for no longer than 3 hours.
Do not freeze mixed NovoSeven® RT solution or store it in syringes.

Keep mixed NovoSeven® RT solution out of direct light.

- If your dose requires more than one vial, repeat step A to J with additional vials, vial adapters and pre-filled syringes until you have reached your required dose.

- Keep the plunger rod pushed completely in.
- Turn the syringe with the vial upside down.
- Stop pushing the plunger rod and let it move back on its own while the mixed solution fills the syringe.
- Pull the plunger rod slightly downwards to draw the mixed solution into the syringe.
- If you only need part of the entire dose, use the scale on the syringe to see how much mixed solution you withdraw, as instructed by your doctor or nurse.
- While holding the vial upside down, tap the syringe gently to let any air bubbles rise to the top.
- Push the plunger rod slowly until all air bubbles are gone.

- Unscrew the vial adapter with the vial.

Caution: The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector. Some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave®/MicroClave®, InVision-Plus®, InVision-Plus® CS®, InVision-Plus® Junior®, Bionector™), and their use can damage the connector and affect administration. To administer product through incompatible needleless connectors, withdraw reconstituted product into a standard 10 ml sterile Luer-lock plastic syringe.

If you have encountered any problems with attaching the pre-filled histidine diluent syringe to any Luer-lock compatible device, please contact Novo Nordisk at (877) 668-6777.