## Dosage and Administration

### For Intravenous Bolus Injection Only

#### Bleeding Episodes (2.1)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hemophilia A or B with Inhibitors</td>
<td>90 mcg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved.</td>
</tr>
<tr>
<td></td>
<td>90 mcg/kg every 3-6 hours after hemostasis is achieved for severe bleeds</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>
</tr>
</tbody>
</table>

#### Peri-operative Management (2.1)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hemophilia A or B with Inhibitors</td>
<td>90 mcg/kg immediately before surgery, repeat every 2 hours during surgery</td>
</tr>
<tr>
<td></td>
<td>90 mcg/kg every 2 hours after surgery for 48 hours, then every 2-6 hours until healing has occurred</td>
</tr>
<tr>
<td>Major</td>
<td>90 mcg/kg immediately before surgery, repeat every 2 hours during surgery</td>
</tr>
<tr>
<td></td>
<td>90 mcg/kg every 2 hours after surgery for 5 days, then every 4 hours until healing has occurred</td>
</tr>
<tr>
<td>Acquired Hemophilia</td>
<td>70-90 mcg/kg immediately before surgery and every 2-3 hours for the duration of surgery and until hemostasis is achieved</td>
</tr>
<tr>
<td>Congenital Factor VII Deficiency</td>
<td>15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of surgery and until hemostasis is achieved</td>
</tr>
<tr>
<td>Glanzmann's Thrombasthenia</td>
<td>90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure</td>
</tr>
<tr>
<td></td>
<td>90 mcg/kg every 2-6 hours to prevent post-operative bleeding</td>
</tr>
</tbody>
</table>

## Full Prescribing Information: Contents*

**1** Indications and Usage

**2** Dosage and Administration

2.1 Dose

2.2 Reconstitution

2.3 Administration

**3** Dosage Forms and Strengths

**4** Contraindications

**5** Warnings and Precautions

5.1 Thrombosis

5.2 Hypersensitivity Reactions

5.3 Antibody Formation in Factor VII Deficient Patients

5.4 Laboratory Tests

**6** Adverse Reactions

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

**7** Drug Interactions

**8** Use in Specific Populations

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

**10** Overdose

**11** Description

**12** Clinical Pharmacology

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

**13** Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

**14** Clinical Studies

14.1 Hemophilia A or B with Inhibitors

14.2 Congenital Factor VII Deficiency

14.3 Acquired Hemophilia

14.4 Glanzmann’s Thrombasthenia

**15** References

**16** How Supplied/Storage and Handling

**17** Patient Counseling Information

*Sections or subsections omitted from the full prescribing information are not listed.*
1 INDICATIONS AND USAGE
NovoSeven® RT, Coagulation Factor VIIa (Recombinant), is 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

• Treatment with NovoSeven® RT should be initiated under the direction 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.

Treatment of Acute Bleeding Episodes
NovoSeven® RT dosing for the treatment of acute bleeding episodes is provided in Table 1.

Table 1: Dosing for Treatment of Acute Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Dose* and Frequency</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hemophilia A or B with Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery</td>
<td>Post surgical: 90 mcg/kg every 2-6 hours until healing occurs</td>
</tr>
<tr>
<td>Major</td>
<td>Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery</td>
<td>Post surgical: 90 mcg/kg every 2-6 hours until healing occurs</td>
</tr>
</tbody>
</table>

*The minimum effective dose has not been determined.

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
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

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Dose* and Frequency</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Hemophilia A or B with Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery</td>
<td>Post surgical: 90 mcg/kg every 2-6 hours until healing occurs</td>
</tr>
<tr>
<td>Major</td>
<td>Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery</td>
<td>Post surgical: 90 mcg/kg every 2-6 hours until healing occurs</td>
</tr>
</tbody>
</table>

*The minimum effective dose has not been determined.

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 containing either 1 histidine diluent vial or 1 vial of histidine diluent.

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 + 1.1 mL Histidine diluent
   2 mg (2000 micrograms) vial + 2.1 mL Histidine diluent
   5 mg (5000 micrograms) vial + 5.2 mL Histidine diluent
   8 mg (8000 micrograms) vial + 8.1 mL Histidine diluent
3. Remove caps from the NovoSeven® RT vials to expose the central portion of the rubber stopper. Cleanse the rubber stoppers with alcohol and allow to dry prior to use.
4. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe. It is recommended to use syringe needles of gauge size 20-26.
5. Insert the needle of the syringe into the Histidine diluent vial. Inject air into the vial and withdraw the quantity required for reconstitution.
6. Insert the syringe needle containing the diluent into the NovoSeven® RT vial through the center of the rubber stopper, aiming the needle against the side so that the stream of liquid runs down the vial wall (the NovoSeven® RT vial does not contain a vacuum). Do not inject the diluent directly on the NovoSeven® RT powder.
7. Gently swirl the vial until all the material is dissolved. The reconstituted solution is a clear, colorless solution which may be stored either at room temperature or refrigerated for up to 3 hours after reconstitution. After reconstitution with the specified volume of diluent, each vial contains approximately 1 mg per mL NovoSeven® RT (1000 micrograms per mL).

NovoSeven® RT package containing 1 vial of NovoSeven® RT powder and 1 pre-filled histidine diluent syringe with vial adapter for needleless reconstitution.

Vial with NovoSeven® RT powder

1. Pre-filled syringe with diluent
2. Vial adapter
3. Protective cap
4. Spine (under protective paper)
5. Protective paper

1. Place the NovoSeven® RT vial on a flat surface. While holding the vial adapter package, place the vial adapter over the NovoSeven® RT vial and press down firmly on the package until the vial adapter spike penetrates the rubber stopper.
NovoSeven® RT Coagulation Factor VIIa (Recombinant)

6. Attach the plunger rod to the syringe. Turn the plunger rod clockwise into the plunger inside the pre-filled diluted syringe until resistance is felt. Remove the syringe cap from the pre-filled diluted syringe and screw onto the vial adapter.

7. Push the plunger rod to slowly inject all the diluted into the vial. Keep the plunger rod pressed down and swirl the vial gently until the powder is dissolved. The reconstituted solution is a clear, colorless solution which may be stored fully assembled either at room temperature or refrigerated for up to 3 hours after reconstitution. After reconstitution with the specified volume of diluent, each vial contains approximately 1 mg per mL NovoSeven® RT (1000 micrograms per mL).

2.3 Administration

For intravenous bolus injection only

- Inspect the reconstituted NovoSeven® RT visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.
- Do not freeze reconstituted NovoSeven® RT or store it in syringes.
- Administer within 3 hours after reconstitution.
- Do not mix with other infusion solutions.
- Discard any unused solution.

Perform the following procedures immediately prior to administration:

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

1. Always use aseptic technique.
2. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
3. Insert needle into the vial of reconstituted NovoSeven® RT. Inject 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 pre-filled histidine-diluent syringe 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 mixed solution is drawn into the intravenous diluent syringe. Tap the syringe to remove air bubbles and withdraw the required dose amount of reconstituted NovoSeven® RT into the syringe.
3. Unscrew the vial adapter with the vial. Discard the empty NovoSeven® RT vial with the vial adapter attached.

Caution:
- The pre-filled diluted 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 diluted 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 diluted syringe to any Luer-lock compatible device, contact Novo Nordisk at (877) 868-6777. Administer NovoSeven® RT using the following procedures:
  - 1. Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.
  - 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) recombinant 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 diluted 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).

4 CONTRAINDICATIONS

None known.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance.
- Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, chronic injury, septicaemia, or coconcurrent treatment with aPCPs/PCCs (activated or nonactivated prothrombin complex concentrates) and uncontrolled post-partum hemorrhage have an increased risk of developing thromboembolic events due to circulating tissue factor (TF) or predisposing coagulopathy (See Adverse Reactions (6.1) and Drug Interactions (7)).

- Exercise caution when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications.

- Do not mix with other infusion solutions.
- Discard any unused solution.
- Do not freeze reconstituted NovoSeven® RT or store it in syringes.

Perform the following procedures immediately prior to administration:

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

1. Always use aseptic technique.
2. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
3. Insert needle into the vial of reconstituted NovoSeven® RT. Inject 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 pre-filled histidine-diluent syringe 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 mixed solution is drawn into the intravenous diluent syringe. Tap the syringe to remove air bubbles and withdraw the required dose amount of reconstituted NovoSeven® RT into the syringe.
3. Unscrew the vial adapter with the vial. Discard the empty NovoSeven® RT vial with the vial adapter attached.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis have been reported with NovoSeven® RT. Monitor patients with NovoSeven® RT for signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory evidence of intravascular coagulation or presence of clinical thrombosis, reduce the dose of NovoSeven® RT or stop the treatment, depending on the patient's condition.

5.3 Antibody Formation in Factor VII Deficient Patients

Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven® RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.

5.4 Laboratory Tests

Laboratory coagulation parameters (PT/INR, aPTT, FVII:C), may give different results with NovoSeven® RT administration is unknown.

PT (sec) PT versus FVII:C

INR: NovoSeven® RT has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NovoSeven® RT on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have been normalized.

aPTT: While administration of NovoSeven®shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds.

FVII:C: FVII:C levels were measured two hours after NovoSeven® administration of 35 micrograms per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

6 ADVERSE REACTIONS

The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® RT in clinical trials occurred in 4% of patients with congenital 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 ≥2% of the patients that were treated with NovoSeven® RT for 1,593 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>Reactions</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>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Platelets, Bleeding, and Clotting</td>
<td>Fibrinolysis decreased</td>
<td>10</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Serious adverse reactions included thrombosis, pain, thrombophile-dips, deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and anaphylaxis, deep vein thrombosis, intracranial thrombosis adverse reaction (n=1), decreased therapeutic response (n=4).

Immunogenicity

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

The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven® RT with the incidence of antibodies to other products may be misleading.

Congenital Factor VII Deficiency

Data collected from the compassionate/use emergency programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that 79 patients with Factor VII deficiency had received NovoSeven® RT. Of these patients for 124 bleeding episodes, surgeries, or prophylaxis, 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).

Immunogenicity

In 73 patients with factor Vll deficiency treated with NovoSeven® RT, one patient developed IgG antibodies against FVII and FVIII. Patients with factor VII deficiency treated with NovoSeven® RT should be monitored for factor VII antibodies.

The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence...
of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven® RT with the incidence of antibodies to other products may be misleading.

Acquired Hemophilia

Data collected from four compassionate use programs, the HTSR registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® RT for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 patients experienced 8 serious adverse reactions. Serious adverse reactions included shock (n=1), cerebrovascular accident (n=1) and thromboembolic events (n=6) which included cerebral arterial occlusion, cerebral ischemia, aneurism pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions were fatal. No new hemostatic pathway was described.

8.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of NovoSeven® RT. 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>
<th>Immune system disorders</th>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (including anaphylactic shock, flushing, urtica, rash, angioedema)</td>
<td>Thromboembolic events (including hepatic artery thrombosis, myocardial infarction, cerebral infarction, intracranial thrombus, peripheral ischemia, portal vein thrombolysis, myocardial ischemia, renal artery thrombosis)</td>
<td></td>
<td></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

Risk Summary

There are no adequate and well-controlled studies using NovoSeven® RT in pregnant women to determine whether there is a drug-associated risk.

Treatment of rats and rabbits with NovoSeven® RT in reproduction studies has been associated with mortality at doses of 10 mg/kg body weight and 5 mg/kg body weight, respectively. At 6 mg/kg body weight in mice, the dose rate was 6/20 mg/kg/day in rabbits at 5 mg/kg body weight, the abortion rate was 25% of 25 litters. Twenty-three out of 25 female rats given 6 mg/kg body weight of NovoSeven® RT gave birth successfully; however, two of the 25 litters died during the early period of lactation. No evidence of triteragonitogen was observed after dosing with NovoSeven® RT.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Breastfeeding

There is no information regarding the presence of NovoSeven® RT in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NovoSeven® RT and any potential adverse effects on the breastfed infant from NovoSeven® RT or from the underlying maternal condition.

8.4 Pediatric Use

Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age.

Hemophagia A or B with Inhibitors

During the investigational phase of product development, hemophagia A or B patients with 6 or 8 or 10 or 12 years for 146 bleeding episodes, 43 children aged 6 to 12 years for 375 bleeding episodes and 30 children aged 12 to 16 years for 446 bleeding episodes.

In a double-blind, randomized comparison trial of two dose levels of NovoSeven® RT in children aged 16 to 24 years and 2 mg/kg dose group and 9/12 (75%) in the 35 mcg/kg dose group at 5 days.

In the surgery trial comparing bolus (BI) and continuous infusion (CI) 100% effective (defined as effective = 99%) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 1/2 (50%) in the 55 mcg/kg dose group.

NovoSeven® RT was used in two trials in surgery. In a dose comparison 22 children aged 0 to 16 years were treated with NovoSeven® RT. Effective intraoperative hemostasis (defined as bleeding that had stopped completely or had decreased substantially [rated as effective = 96%] or bleeding that was reduced but continued [rated as partially effective = 9%]) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 1/2 (50%) in the 55 mcg/kg dose group at 5 days.

There were no serious adverse reactions in the trial comparing bolus and continuous infusion. In the bolus group, 2/12 (17%) patients had serious adverse reactions, 1 with sepsis and 1 with meningitis. In the continuous infusion group, 0/10 (0%) patients had serious adverse reactions.

In the surgery trial comparing bolus (BI) and continuous infusion (CI) 6 children aged 10 to 15 years participated, 3 in each group. Both regimens were 100% effective (defined as bleeding has stopped completely or has decreased substantially [rated as effective = 96%] or bleeding that was reduced but continued [rated as partially effective = 9%]) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 1/2 (50%) in the 55 mcg/kg dose group at 5 days.

NovoSeven® RT was used in four children aged 6 months to 1 year (2 with congenital factor VII deficiency and 2 with acquired factor VII deficiency) for bleeding episodes in children aged 0 to 12 years and >12 to 16 years. The following are examples of accidental overdose.

The diluent for reconstitution of NovoSeven® RT is a 10 molar solution of histidine in water for injection and is supplied as a clear colorless solution in a vial or pre-filled diluer syringe. After reconstitution with the appropriate volume of histidine, each vial contains approximately 1 mg/mL NovoSeven® RT (corresponding to 1000 micrograms/mL). The reconstituted solution is a clear colorless solution with a pH of approximately 6.0 and contains no preservatives.

Recombinant coagulation Factor V (rFV), the active ingredient in NovoSeven® RT, is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues with an approximate molecular mass of 45 kDa. It is structurally similar to endogenous human coagulation factor Vila.

The gene for human coagulation factor VII (FVII) is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autotaxis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MULv, S404, Pox virus, Reovirus). Human or other sera proteins are used in the production or formulation of NovoSeven® RT.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NovoSeven® RT is recombinant Factor Vila and, when complexed with tissue factor can activate coagulation Factor X to Factor xa, as well as coagulation Factor IX to Factor Xa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.

12.2 Pharmacodynamics

The effect of NovoSeven® RT upon coagulation in patients with or without hemophilia has been assessed in different model systems. In an in vitro model of tissue-factor-initiated blood coagulation (Figure A), the addition of rFVIIa increased both the rate and level of thrombin generation in normal and hemophilia A blood, with an effect shown at rFVIIa concentrations as low as 10 nM. 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 demonstrated 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/microliter. Coagulation was 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.
**13 NONCLINICAL TOXICOLOGY**

Two murine studies have given no indication of carcinogenic potential for NovoSeven®. The clastogenic activity of NovoSeven® was evaluated in both in vitro studies (i.e., human lymphocytes) and in vivo studies (i.e., mouse micronucleus test). Neither of these studies indicated clastogenic activity of NovoSeven®. Other genotoxicity studies have not been performed with NovoSeven® RT (e.g., Ames test). No chronic carcinogenicity studies have been performed with NovoSeven® RT.

Note: The clinical pharmacokinetic study was not performed with NovoSeven® RT.

**1.2 Animal Toxicology and/or Pharmacology**

In a monkey cardiovascular safety pharmacology model evaluating the combination of excessive doses of Coagulation Factor XIII A-Subunit (Recombinant) (585 IU/kg, 17 times the expected human dose) and NovoSeven® RT (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 6 indwelling catheters per monkey and the induction of anesthetics, 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 rFXII and NovoSeven® RT at recommended wound healing 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® during the investigational phase of product development were in an open protocol study,[8,9] that began enrollment in 1988, shortly after the completion of a pharmacokinetic study. The cohort included persons with hemophilia types A or B (with or without inhibitors), persons with acquired inhibitors to Factor VIII or Factor IX, and a few FVII deficient patients. The clinical situations were diverse including difficulty in maintaining a satisfactory level of factor VII, surgical prophylaxis, intrauterine bleeding, and other emergent situations.

A double-blind, randomized comparison trial of two dose levels of NovoSeven® in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors was conducted in 78 patients who received NovoSeven® in treatment centers within 4 to 18 hours after experiencing a bleed. Thirty-five patients were treated at the 35 mcg/kg per dose (50 mg/kg bolus dose and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 mcg/kg per dose (60 joint and 14 muscle bleeding episodes). Dosing was repeated at 2.5 hour intervals but ranged up to four hours for some patients. Efficacy was assessed after 2.5 hours and at the end of treatment, whichever occurred first. Based on a subjective evaluation by the investigator, the efficacy response rates for the 35 and 70 mcg/kg per dose groups were: excellent (definite relief of pain/tenderness as reported by the patient, with little or no residual pain and no further bleeding) in 85/115 (74%) and 110/151 (73%), respectively; partial (definite relief of pain/tenderness as reported by the patient and/or a measurable decrease of the size of the hemorrhage and/or arrest of bleeding within 6 hours) in 18/115 (16%) and 17/151 (11%), respectively.

**14.2 Concomitant 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 the GTR, 57 in the compassionate use program, and 22 in the 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 medication therapy); and 3 were from a registry maintained by the Hemophilia and Thrombosis Research Society (HTRS) registry. 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. Sixty-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 (6 non-surgical, 3 surgical and 2 episodes classified as other). Concomitant use of other hemostatic agents was not significant in 20 cases (41, 13%); 19 patients (39%) received one other hemostatic agent. The most common hemostatic agents used were antifibrinolytics, Factor VIII and activated prothrombin complex concentrates.

The median dose of NovoSeven® administered was 90 micrograms per kg (range: 31 to 197 micrograms per kg); the mean number of injections per day was 6 (range: 1 to 10 injections per day). Overall efficacy (i.e., effective and partially effective outcomes) was 87/112 (78%), with 77/100 (77%) efficacy in the compassionate use program and 10/12 (83%) efficacy in the HTRS registry. In the compassionate use programs, overall efficacy for the first-line treatment was 38/44 (86%) compared to 39/56 (70%) when used as salvage treatment (Table 8).

### Table 8: Efficacy by Dose Group, for Patients Receiving Doses Ranging from <61 to >90 micrograms/kg

<table>
<thead>
<tr>
<th>Dose Group</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>&lt;61 micrograms/kg</td>
<td>92</td>
<td>266</td>
<td>251 (94.4%)</td>
<td>4 (1.5%)</td>
<td>6 (2.3%)</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>61-70 micrograms/kg</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>71-80 micrograms/kg</td>
<td>69</td>
<td>157</td>
<td>150 (95.5%)</td>
<td>2 (1.2%)</td>
<td>2 (1.3%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>&gt;90 micrograms/kg</td>
<td>218</td>
<td>1073</td>
<td>1026 (96.3%)</td>
<td>27 (2.5%)</td>
<td>7 (0.7%)</td>
<td>2 (0.2%)</td>
</tr>
</tbody>
</table>

* All treatment regimens that included treatment with NovoSeven®<sup>b</sup> included GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies
* Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractoriness status unknown
* Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractoriness status
* Treatment was NovoSeven® only for 26/79 episodes with refractoriness with or without antibodies, 2/10 episodes with platelet specific antibodies only, and 61/177 episodes with neither or unknown. The remainder received NovoSeven® with platelets and/or antifibrinolytic agents.

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

<table>
<thead>
<tr>
<th>By 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 (1.2%)</td>
<td>2 (1.3%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Refractoriness ± Platelet-specific antibodies&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>177</td>
<td>166 (98.8%)</td>
<td>2 (1.1%)</td>
<td>4 (2.3%)</td>
<td>5 (2.6%)</td>
<td></td>
</tr>
</tbody>
</table>

* All treatment regimens that included treatment with NovoSeven® included GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies
* Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractoriness status unknown
* Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractoriness status
* Treatment was NovoSeven® only for 22/70 episodes with refractoriness with or without antibodies, 13/24 episodes with platelet specific antibodies only, and 61/177 episodes with neither or unknown. The remainder received NovoSeven® with platelets and/or antifibrinolytic agents.

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

<table>
<thead>
<tr>
<th>By Antibody/Refractory Group</th>
<th>No. of patients</th>
<th>No. of procedures</th>
<th>Success</th>
<th>Insufficient data</th>
</tr>
</thead>
<tbody>
<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>94</td>
<td>94</td>
<td>94 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Refractoriness ± Platelet-specific antibodies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33</td>
<td>70</td>
<td>69 (98.6%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Platelet-specific antibodies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>24</td>
<td>24 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Neither or unknown&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36</td>
<td>66</td>
<td>66 (100%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

* All treatment regimens that included treatment with NovoSeven® included GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies
* Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractoriness status unknown
* Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractoriness status
* Treatment was NovoSeven® only for 22/70 episodes with refractoriness with or without antibodies, 13/24 episodes with platelet specific antibodies only, and 61/177 episodes with neither or unknown. The remainder received NovoSeven® with platelets and/or antifibrinolytic agents.

In HTRS, there were 7 patients that were treated with NovoSeven® for 4 bleeding episodes. Concomitant hemostatic agents were administered for 11 episodes (antifibrinolytics in 10 episodes). Treatment was reported effective in 21 of 23 (91.3%) episodes. In the other 2 episodes, bleeding was reported as slowed or no improvement; however in neither episode was further treatment reported. There were no surgical procedures reported in the HTRS registry.

### 15 REFERENCES

4. Fildes A. Copyright American Society of Haematology, used with permission.
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, one vial per carton. The diluent for reconstitution of 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.

- NovoSeven® RT powder and histidine diluent vials are made of glass, with a siliconised bromobutyl 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.

- NovoSeven® RT powder and histidine diluent syringes are equipped with a tamper-evident rubber plunger not made with natural rubber latex.

- NovoSeven® RT either at room temperature or refrigerated for up to 3 hours. Do not freeze. Store protected from light. Do not use past the expiration date.

17 PATIENT COUNSELING INFORMATION

- Advise patients to read the FDA-approved patient labeling (Instructions for Use).
- Advise patients about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
- Advise patients to immediately seek medical help if any of the above signs or symptoms occur.
- Advise patients to follow the recommendations in the FDA-approved patient labeling, regarding proper sharps disposal.

<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 7010 01 | NovoSeven® RT in a single-use vial (NDC 0169-7017-11)  
Histidine diluent in vial, 1.1 mL  
NDC (0169-7001-98) |
| 2 mg per vial (2000 micrograms/vial) | NDC 0169 7020 01 | NovoSeven® RT in a single-use vial (NDC 0169-7027-11)  
Histidine diluent in vial, 2.1 mL  
NDC (0169-7002-98) |
| 5 mg per vial (5000 micrograms/vial) | NDC 0169 7050 01 | NovoSeven® RT in a single-use vial (NDC 0169-7057-11)  
Histidine diluent in vial, 5.2 mL  
NDC (0169-7005-98) |
| 8 mg per vial (8000 micrograms/vial) | NDC 0169 7040 01 | NovoSeven® RT in a single-use vial (NDC 0169-7047-11)  
Histidine diluent in vial, 8.1 mL  
NDC (0169-7004-98) |

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.
NovoSeven® RT, Coagulation Factor VIIa (Recombinant)

FDA-approved patient labeling
Instructions for Use
NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Instructions on how to use NovoSeven® RT
READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NOVOSEVEN® RT.

NovoSeven® RT is supplied as a powder. Before injection (administration) it must be mixed (reconstituted) with the liquid diluent supplied in the syringe. The liquid diluent is a histidine solution. The mixed NovoSeven® RT must be injected into your vein (intravenous injection). The equipment in this package is designed to mix and inject NovoSeven® RT.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads, and bandages.

Don’t use the equipment without proper training from your doctor or nurse. Always use a clean and germ free (aseptic) technique. It is important that you wash your hands and ensure that the area around you is clean.

Don’t open the equipment until you are ready to use it. The equipment is for single use only.

Content
The package contains:
• Vial with NovoSeven® RT powder
• Vial adapter
• Pre-filled syringe with diluent
• Plunger rod (placed under the syringe)

Overview
Vial with NovoSeven® RT powder
Vial adapter

1. Prepare the vial and the syringe
   • Take out the number of NovoSeven® RT packages you need. Check the expiry 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 take 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.
   • Place the vial on a flat and solid surface.
   • Turn over the protective cap, and snap the vial adapter onto the vial.
   • Don’t touch the spike on the vial adapter.
   • Once attached, don’t remove the vial adapter from the vial.

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 the syringe cap.
   • If the syringe cap is loose or missing, don’t use the pre-filled syringe.
   • Screw the pre-filled syringe securely onto the vial adapter until resistance is felt.
   • Avoid touching the sides of the plunger rod at any time.

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.
   • Keep the plunger rod pressed down and swirl the vial gently until all the powder is dissolved. Don’t shake the vial as this will cause foaming.
   • Check the mixed solution.
   • It must be clear and colorless. If you notice visible particles or discoloration, don’t use it. Use a new package instead.

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®, Bioclave®), 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.

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.
   • Keep mixed NovoSeven® RT solution out of direct light.

Keep your patient well hydrated and monitored closely. 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.
• Grasp the vial adapter and let it move back on its own while the mixed solution fills the syringe.
• UnScrew the vial adapter with the vial.

Unscrew the vial adapter from the vial adapter and the syringe attached, at room temperature or refrigerated for no longer than 3 hours.

Don’t throw it out with the ordinary household trash.

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.

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.

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 disassemble the vial and vial adapter before disposal.

Don’t reuse the equipment.