

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 NovoSeven® RT.

NovoSeven® RT, Coagulation Factor VIIa (Recombinant) For Intravenous Use Only. Lyophilized Powder for Solution for Injection
Initial U.S. Approval: 1999

WARNING: THROMBOSIS

See full prescribing information for complete boxed warning

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported. (5.1)
- 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. (5.1)

INDICATIONS AND USAGE

NovoSeven® RT, Coagulation Factor VIIa (Recombinant) is indicated for:

- Treatment of bleeding episodes and perioperative 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 perioperative management in adults with acquired hemophilia (1)

DOSAGE AND ADMINISTRATION

For intravenous bolus injection only

Bleeding Episodes (2.1)

Indication	Dosing Recommendation
Congenital Hemophilia A or B with Inhibitors	<ul style="list-style-type: none"> • 90 mcg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved • 90 mcg/kg every 3-6 hours after hemostasis is achieved for severe bleeds
Acquired Hemophilia	• 70-90 mcg/kg every 2-3 hours until hemostasis is achieved
Congenital Factor VII Deficiency	• 15-30 mcg/kg every 4-6 hours until hemostasis is achieved
Glanzmann's Thrombasthenia	• 90 mcg/kg every 2-6 hours until hemostasis is achieved

Peri-operative Management (2.1)

Indication	Dosing Recommendation
Congenital Hemophilia A or B with Inhibitors	<p>Minor:</p> <ul style="list-style-type: none"> • 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery • 90 mcg/kg every 2 hours after surgery for 48 hours, then every 2-6 hours until healing has occurred <p>Major:</p> <ul style="list-style-type: none"> • 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery • 90 mcg/kg every 2 hours after surgery for 5 days, then every 4 hours until healing has occurred
Acquired Hemophilia	• 70-90 mcg/kg immediately before surgery and every 2-3 hours for the duration of surgery and until hemostasis is achieved
Congenital Factor VII Deficiency	• 15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of surgery and until hemostasis is achieved
Glanzmann's Thrombasthenia	<ul style="list-style-type: none"> • 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure • 90 mcg/kg every 2-6 hours to prevent post-operative bleeding

DOSAGE FORMS AND STRENGTHS

Available as lyophilized powder in single-use vials of 1, 2, 5, or 8 mg recombinant coagulation factor VIIa (FVIIa). After reconstitution with specified volume of histidine diluent, the final solution contains 1 mg per mL (1000 micrograms per mL) of recombinant FVIIa (3)

CONTRAINDICATIONS

None known (4)

WARNINGS AND PRECAUTIONS

- Serious arterial and venous thrombotic events may occur (5.1)
- Hypersensitivity reactions have been reported. Anaphylaxis and other hypersensitivity reactions may occur. Should symptoms occur, discontinue NovoSeven® RT and administer appropriate treatment (5.2)
- Monitor Factor VII deficient patients for prothrombin time (PT) and FVII coagulant activity, and for antibody formation to NovoSeven® RT (5.3)

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 administer NovoSeven® RT with coagulation factor XIII (FXIII) (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2017

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS

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

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

Dose* and Frequency	Duration of Therapy	Additional Information
Congenital Hemophilia A or B with Inhibitors		
Hemostatic 90 mcg/kg every two hours, adjustable based on severity of bleeding	Until hemostasis is achieved, or until the treatment has been judged to be inadequate	The appropriate duration of post-hemostatic dosing has not been studied
Post-Hemostatic 90 mcg/kg every 3-6 hours for severe bleeds	After hemostasis is achieved to maintain the hemostatic plug	
Acquired Hemophilia		
70-90 mcg/kg every 2-3 hours	Until hemostasis is achieved	
Congenital Factor VII Deficiency		
15-30 mcg/kg every 4-6 hours	Until hemostasis is achieved	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight. Adjust dose and frequency of injections to each individual patient
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

*The minimum effective dose has not been determined

Congenital Hemophilia A or B with inhibitors

- Dose and administration interval may be adjusted to the individual patient based on the severity of the bleeding.¹

- 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

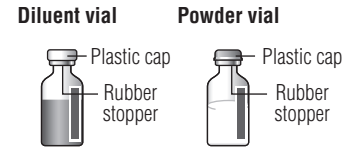
Type of Surgery	Dose and Frequency	Additional Information
Congenital Hemophilia A or B with Inhibitors		
Minor	Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery Post surgical: 90 mcg/kg every 2 hours for 48 hours then every 2-6 hours until healing occurs	
Major	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 for 5 days then every 4 hours until healing occurs	Additional bolus doses should be administered if required
Acquired Hemophilia		
Minor or Major	70-90 mcg/kg immediately before surgery and repeat every 2-3 hours for the duration of the surgery and until hemostasis is achieved*	
Congenital Factor VII Deficiency		
Minor or Major	15-30 mcg/kg immediately before surgery and repeat every 4-6 hours for the duration of the surgery and until hemostasis is achieved* Adjust dose and frequency of injections to each individual patient	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight
Glanzmann's Thrombasthenia		
Minor or Major	Initial: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure* Post surgical: 90 mcg/kg every 2-6 hours to prevent post-operative bleeding*	Higher average infused doses (median dose was 100 micrograms per kg (IQR 90-140)) were noted for surgical patients who had clinical refractoriness with or without platelet-specific antibodies compared to those with neither

*The minimum effective dose has not been determined.

2.2 Reconstitution

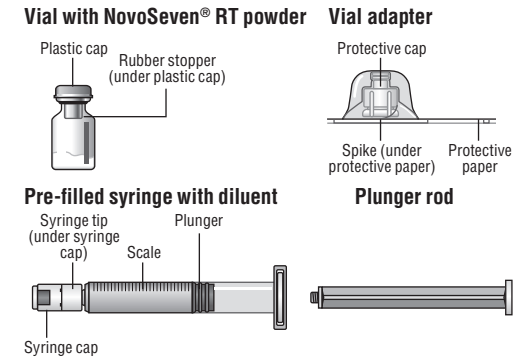
- Follow the procedures below for the preparation and reconstitution of NovoSeven® RT. For questions regarding reconstitution, please contact Novo Nordisk at 1-877-NOVO-777.
- Calculate the NovoSeven® RT dosage and select the appropriate NovoSeven® RT package provided with either 1 histidine diluent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

NovoSeven® RT package containing 1 vial of NovoSeven® RT powder and 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 an alcohol swab 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:



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 in pre-filled syringe
2 mg (2000 micrograms) vial + 2 mL Histidine diluent in pre-filled syringe
5 mg (5000 micrograms) vial + 5 mL Histidine diluent in pre-filled syringe
8 mg (8000 micrograms) vial + 8 mL Histidine diluent in pre-filled syringe
3. Remove cap from the NovoSeven® RT vial. Cleanse the rubber stopper with an alcohol swab and allow to dry prior to use.
4. Peel back the protective paper from the vial adapter. Do not remove the vial adapter from the package.
5. 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.

- Attach the plunger rod to the syringe. Turn the plunger rod clockwise into the plunger inside the pre-filled diluent syringe until resistance is felt. Remove the syringe cap from the pre-filled diluent syringe and screw onto the vial adapter.
- Push the plunger rod to slowly inject all the diluent 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:

- Always use aseptic technique.
- Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
- 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.
- 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:

- Always use aseptic technique.
- Invert the NovoSeven® RT vial. 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. Tap the syringe to remove air bubbles and withdraw the required dose amount of reconstituted NovoSeven® RT into the syringe.
- Unscrew 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.
- 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.

Administer NovoSeven® RT using the following procedures:

- Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.
- If line needs to be flushed before or after NovoSeven® RT administration, use 0.9% Sodium Chloride Injection, USP.
- 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 (rFVIIa) 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).

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, crush injury, septicemia, or concomitant treatment with aPCCs/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. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications.
- Monitor patients who receive NovoSeven® RT for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of NovoSeven® RT or stop the treatment, depending on the patient's condition.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis have been reported with NovoSeven® RT. Administer NovoSeven® RT only if clearly needed in patients with known hypersensitivity to NovoSeven® RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins. Should symptoms occur, discontinue NovoSeven® RT, administer appropriate treatment and weigh the benefit/risks prior to restarting treatment with NovoSeven® RT.

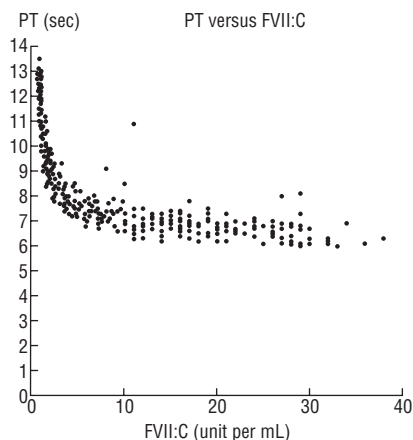
5.3 Antibody Formation in Factor VII Deficient Patients

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, or 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) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven® has been shown to produce the following characteristics:

PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 units per mL. For FVII:C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven® RT administration is unknown.



INR: NovoSeven® 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® 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 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.

FVIIa:C: FVIIa: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® 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 ≥2% 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

Body System	# of adverse reactions (n=1,939 treatments)	# of patients (n=298 patients)
Reactions		
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Fibrinogen plasma decreased	10	5
Cardiovascular		
Hypertension	9	6

Serious adverse reactions included thrombosis, pain, thrombophlebitis deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and abnormal hepatic function. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome.

In two clinical trials evaluating safety and efficacy of NovoSeven® administration in the perioperative setting in hemophilia A or B patients with inhibitors (N=51), the following serious adverse reactions were reported: acute post-operative hemothrosis (n=1), internal jugular thrombosis adverse reaction (n=1), decreased therapeutic response (n=4).

Immunogenicity

There have been no confirmed reports of inhibitory antibodies against NovoSeven® or FVII 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/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society² (HTRS) registry showed that 75 patients with Factor VII deficiency had received NovoSeven®: 70 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 rFVIIa and FVII (n=1), localized phlebitis (n=1).

Immunogenicity

In 75 patients with factor FVII deficiency treated with NovoSeven® RT, one patient developed IgG antibody against rFVIIa and FVII. 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 HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® 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 artery occlusion, cerebral ischemia, angina pectoris, myocardial 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

MedDRA System Organ Class	Preferred Term
Immune system disorders	Hypersensitivity (including anaphylactic shock, flushing, urticaria, rash, angioedema)
Vascular disorders	Thromboembolic events (including hepatic artery thrombosis, myocardial infarction, cerebral infarction, intestinal infarction, intracardiac thrombus, peripheral ischemia, portal vein thrombosis, myocardial ischemia, renal artery thrombosis)

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® in reproduction studies has been associated with mortality at doses up to 6 mg per kg body weight and 5 mg per kg body weight respectively. At 6 mg per kg body weight in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg body weight, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg per kg body weight 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®.

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

8.2 Lactation

Risk Summary

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.

Hemophilia A or B with Inhibitors

During the investigational phase of product development NovoSeven® was used in 16 children aged 0 to <2 years for 151 bleeding episodes, 27 children aged 2 to <6 years for 140 bleeding episodes, 43 children aged 6 to <12 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® in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors 20 children aged 0 to <12 and 8 children aged 12 to 16 were treated with NovoSeven® in doses of 35 or 70 micrograms per kg dose. Treatment was assessed as effective (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 8 hours [rated as excellent = 51%], within 8-14 hours [rated as effective = 18%] or after 14 hours [rated as partially effective = 25%]) in 94% of the patients.

NovoSeven® was used in two trials in surgery. In a dose comparison 22 children aged 0 to 16 years were treated with NovoSeven®. Effective intraoperative hemostasis (defined as bleeding that had stopped completely or had decreased substantially [rated as effective = 86%] 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 10/12 (83%) in the 35 mcg/kg dose group at 48 hours; effective hemostasis was achieved in 10/10 (100%) in the 90 mcg/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) 6 children aged 10 to 15 years participated, 3 in each group. Both regimens were 100% effective (defined as bleeding has stopped completely, or decreased substantially) intra-operatively, through the first 24 hours and at day 5. At the end of the study period (Postoperative day 10 or discontinuation of therapy) hemostasis in two patients in the BI group was rated effective and hemostasis in one patient was rated as ineffective (defined as bleeding is the same or has worsened). Hemostasis in all three patients in the CI group was rated as effective.

Adverse drug reactions in pediatric patients were similar to those previously reported in clinical trials with NovoSeven®, including one thrombotic event in a 4 year old with internal jugular vein thrombosis after port-a-cath placement which resolved.

Congenital Factor VII deficiency

In published literature, compassionate use trials and registries on use of NovoSeven® in congenital Factor VII deficiency, NovoSeven® was used in 24 children aged 0 to <12 years and 7 children aged 12 to 16 years for 38 bleeding episodes, 16 surgeries and 8 prophylaxis regimens. Treatment was effective in 95% of bleeding episodes (5% not rated) and 100% of surgeries. No thrombotic events were reported. A seven-month old exposed to NovoSeven® and various plasma products developed antibodies against FVII and rFVIIa [see *Adverse Reactions* (6.1) and *Overdosage* (10)].

Glanzmann's Thrombasthenia

In the Glanzmann's Thrombasthenia Registry, NovoSeven® was used in 43 children aged 0 to 12 years for 157 bleeding episodes and in 15 children aged 0 to 12 years for 19 surgical procedures. NovoSeven® was also used in 8 children aged >12 to 16 years for 17 bleeding episodes and in 3 children aged >12 to 16 years for 3 surgical procedures. Efficacy of regimens including NovoSeven® was evaluated by independent adjudicators as 93.6% and 100% for bleeding episodes in children aged 0 to 12 years and >12 to 16 years, respectively. Efficacy in surgical procedures was evaluated as 100% for all surgical procedures in children aged 0 to 16 years. No adverse reactions were reported in Glanzmann's thrombasthenia children. [See *Clinical Studies* (14)]

8.5 Geriatric Use

Clinical studies of NovoSeven® RT in congenital factor deficiencies and Glanzmann's thrombasthenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Dose limiting toxicities of NovoSeven® RT have not been investigated in clinical trials. The following are examples of accidental overdose.

- One newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven® (single dose: 800 micrograms per kg body weight). Following additional administration of NovoSeven® and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported.
- One Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms per kg body weight (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke).
- One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received

doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days.

There were no reported complications in either case.

11 DESCRIPTION

NovoSeven® RT, Coagulation Factor VIIa (Recombinant) is a sterile, white lyophilized powder of recombinant human coagulation factor VIIa (rFVIIa) for reconstitution for intravenous injection. The product is supplied as single-use vials containing the following:

Contents	1 mg Vial	2 mg Vial	5 mg Vial	8 mg Vial
rFVIIa	1000 micrograms	2000 micrograms	5000 micrograms	8000 micrograms
sodium chloride*	2.34 mg	4.68 mg	11.7 mg	18.72 mg
calcium chloride dihydrate*	1.47 mg	2.94 mg	7.35 mg	11.76 mg
Glycylglycine	1.32 mg	2.64 mg	6.60 mg	10.56 mg
polysorbate 80	0.07 mg	0.14 mg	0.35 mg	0.56 mg
Mannitol	25 mg	50 mg	125 mg	200 mg
Sucrose	10 mg	20 mg	50 mg	80 mg
Methionine	0.5 mg	1.0 mg	2.5 mg	4 mg

* per mg of rFVIIa: 0.4 mEq sodium, 0.01 mEq calcium

NovoSeven® RT also contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19 ng/mg).

The diluent for reconstitution of NovoSeven® RT is a 10 mmol solution of histidine in water for injection and is supplied as a clear colorless solution in a vial or pre-filled diluent syringe. After reconstitution with the appropriate volume of histidine diluent, 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 VIIa (rFVIIa), the active ingredient in NovoSeven® RT, is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues with an approximate molecular mass of 50 kDa. It is structurally similar to endogenous human coagulation factor VIIa.

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 autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of NovoSeven® RT.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

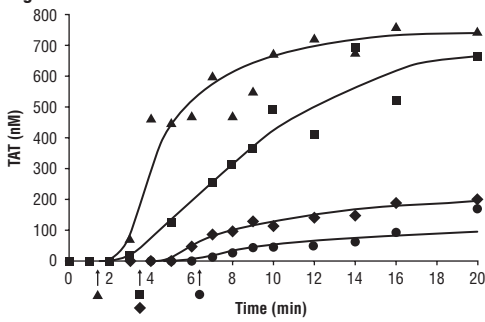
NovoSeven® RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic 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),³ 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.

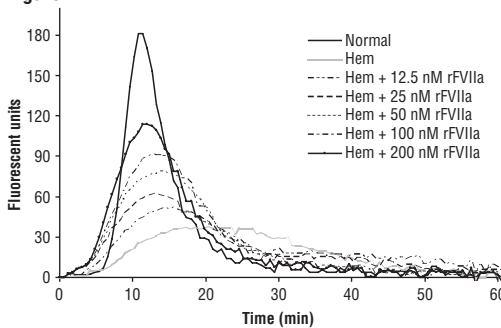
In a separate model, and in line with previous reports,⁴ escalating doses of rFVIIa in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/microliter. 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.

Figure A



TF-initiated clotting of normal blood and congenital hemophilia A blood in the presence of factor VIIa.
Clotting of CTI-inhibited (0.1 mg/mL) normal blood initiated with 12.5 pM TF (■) and addition of 10 nM factor VIIa (▲) and of hemophilia A blood with (◆) and without (●) addition of 10 nM factor VIIa. Figure A shows Thrombin Anti-Thrombin generation over time. Arrows indicate clotting times.

Figure B



TF-initiated clotting of normal and hemophilia A platelet rich plasma in the presence of rFVIIa.

12.3 Pharmacokinetics

Healthy Subjects

The pharmacokinetics of NovoSeven® was investigated in 35 healthy Caucasian and Japanese subjects in a dose-escalation study. Subjects were stratified according to gender and ethnic group and dosed with 40, 80 and 160 micrograms per kg NovoSeven®.⁵ Range of mean results across dose groups and ethnicity (Caucasian, Japanese) are shown in Table 5.

The products NovoSeven® and NovoSeven® RT are pharmacokinetically equivalent in a study of 22 patients receiving single doses of both formulations.⁶ Mean results are shown in Table 5.

Hemophilia A or B

Single dose pharmacokinetics of NovoSeven® (17.5, 35, and 70 micrograms per kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B in non-bleeding and bleeding state.⁷ Median results (non-bleeding state) are shown in Table 5. Incremental recovery was 45.63%. In a bolus single-dose pharmacokinetic study, 5 male adults (90 micrograms per kg) and 10 male pediatric (2-12 years) patients (crossover, 90 and 180 micrograms per kg) with severe hemophilia A (10 of 18 subjects had inhibitors) received NovoSeven®.⁸ The PK of rFVII following 90 and 180 micrograms per kg IV dose in children indicated dose linearity. Results are shown in Table 5.

Congenital Factor VII deficiency

Single dose pharmacokinetics of NovoSeven® in 5 patients with severe congenital Factor VII deficiency (<1%), at doses of 15 and 30 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 18.9% (0.44 U/dl/U/kg) and 22.2% (0.51 U/dl/U/kg) with 15 and 30 micrograms per kg doses. No adverse reactions were reported in the pharmacokinetics for congenital factor VII deficiency.

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.⁹ 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, since the mean plasma recovery for NovoSeven® is 20% for FVII-deficient patients, a NovoSeven® RT dose range of 16-27 micrograms per kg would be required to achieve sufficient FVII plasma levels for hemostasis, which is consistent with the recommended dose range.

Table 5: Single Dose Pharmacokinetic Parameters

Formulation (n)	Healthy Subjects			Hemophilia A or B		FVII Deficiency ¹⁰	
	rFVIIa (n=35) ⁵	rFVIIa (n=22) ⁶	rFVIIa-25C (n=22) ⁶	rFVIIa (n=15) ⁷	rFVIIa (n=10) ⁸	rFVIIa (n=5) ¹⁰	
Ages	20-45	22-44	22-44	15-63	30-45	2-12	20-43
Doses (mcg/kg)	40, 80, 160	90	90	17.5, 35, 70	90	90*, 180	15, 30
CL (mL/h/kg)	33-37	37.63	40.43	31.00	39	58	70.8, 79.1
t _{1/2} (h)	3.9-6.0	3.48	3.54	2.89	3.1	2.6	2.82, 3.11
V _{ss} (mL/kg)	130-165	111.31	122.96	106.5	128	164	280, 290
MRT (h)	ND	2.97	3.05	3.44	3.3	2.8	3.80, 3.75

*Based upon the 90 mcg/kg dose

AUC Area under the curve, CL Clearance, t_{1/2} terminal half-life, V_{ss} 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 evaluated in both *in vitro* studies (i.e., cultured human lymphocytes) and *in vivo* studies (i.e., mouse micronucleus test). Neither of these studies indicated clastogenic activity of NovoSeven®. Other gene mutation studies have not been performed with NovoSeven® RT (e.g., Ames test). No chronic carcinogenicity studies have been performed with NovoSeven® RT.

A reproductive study in male and female rats at dose levels up to 3.0 mg per kg per day had no effect on mating performance, fertility, or litter characteristics.

Treatment of rats and rabbits with NovoSeven® in reproduction studies has been associated with mortality at doses up to 6 mg per kg and 5 mg per kg. At 6 mg per kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg 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 combination of excessive doses of Coagulation Factor XIII A-Subunit (Recombinant) (585 IU/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 6 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 rFVIII 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® during the investigational phase of product development were in an open protocol study^{11,12} that began enrollment in 1988, shortly after the completion of the pharmacokinetic study. These patients 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 and included muscle/joint bleeds, mucocutaneous bleeds, surgical prophylaxis, intracerebral bleeds, and other emergent situations.

A double-blind, randomized comparison trial¹⁴ 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 micrograms per kg dose (59 joint, 15 muscle and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 micrograms per kg dose (85 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 at 12 ± 2 hours or at end of treatment, whichever occurred first. Based on a subjective evaluation by the investigator, the respective efficacy rates for the 35 and 70 micrograms per kg groups were: excellent (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 8 hours) 59% and 60%, effective (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 8-14 hours) 12% and 11%, and partially effective (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 after 14 hours) 17% and 20%. The average number of injections required to achieve hemostasis was 2.8 and 3.2 for the 35 and 70 micrograms per kg groups, respectively.

Two clinical trials were conducted to evaluate the safety and efficacy of NovoSeven® administration during and after surgery in hemophilia A or B patients with inhibitors. One of the studies was a randomized, double-blind, parallel group clinical trial (28 patients with hemophilia A or B and inhibitors and one patient with acquired inhibitor to FVIII, undergoing major or minor surgical procedures).¹⁵ Patients received bolus intravenous NovoSeven® (either 35 micrograms per kg, N=15; or 90 micrograms per kg, N=14) prior to surgery, intra-operatively as required, then every 2 hours for the following 48 hours beginning at closure of the wound. Additional doses were administered every 2 to 6 hours up to an additional 3 days to maintain hemostasis. After a maximum of 5 days of double-blind treatment, therapy could be continued in an open-label manner if necessary (90 micrograms per kg NovoSeven® every 2-6 hours) (Table 6). Efficacy was assessed during the intra-operative period, and post-operatively from the time of wound closure (Hour 0) through Day 5.

Table 6: Dosing by Surgery Category

	Major Surgery		Minor Surgery	
	35 µg/kg* (n=5)	90 µg/kg (n=6)	35 µg/kg (n=10)	90 µg/kg (n=8)
Days of dosing, median (range)	15 (2-26)	9.5 (8-17)	4 (3-6)	6 (3-13)
No. injections, median (range)	135 (11-186)	81 (71-128)	29.5 (24-44)	39.5 (26-98)
Median total dose, mg (range)	656 (31-839)	569 (107-698)	45.5 (14-171)	67 (31-122)

* µg/kg = micrograms per kg body weight

Intraoperative hemostasis was achieved in 28/29 (97%) patients. Satisfactory hemostasis was achieved in 14/14 (100%) patients in the 90 mcg/kg dose group and 11/15 (73%) in the 35 mcg/kg dose group at 48 hours; satisfactory hemostasis was achieved in 13/14 (93%) in the 90 mcg/kg dose group and 11/15 (73%) in the 35 mcg/kg dose group at 5 days. Twenty-three patients successfully completed the entire study including 13/14 (93%) achieving successful hemostasis through study completion (up to day 26) in the 90 mcg/kg dose group.

Another open-label, randomized, parallel trial was conducted to compare the safety and efficacy of bolus intravenous (BI) injection (N=12) and continuous intravenous (CI) infusion (N=12) administration of NovoSeven® in 23 hemophilia A or B patients with inhibitors and one patient with acquired hemophilia who were undergoing elective major surgery. Table 7 provides the overview of dosing by treatment group for BI and CI.

Table 7: Dosing by Treatment Group

	Bolus Injection 90 micrograms/kg (n=12) ^a	Continuous Infusion 50 micrograms/kg/h (n=12)
Days of dosing, median (range)	10 (4-15) ^b	10 (2-116)
No. bolus injections, median (range)	38 (36-42)	1.5 (0-7)
No. of additional bolus injections, median (range)	0 (0-3)	0 (0-4)
Mean total dose, mg	237.5	292.2

^a Includes one patient with acquired hemophilia

^b Includes dosing during the follow-up period after the 10-day study period.

Intraoperative hemostasis was reported as effective in all BI and CI treated patients. BI regimen was 100% effective through the first 24 hours, and was 92% effective at day 5. CI regimen was 83% effective through the first 24 hours, and was 83% effective at day 5. At the end of the study period (Post operative day 10 or discontinuation of therapy), hemostatic efficacy in the BI and CI arms was 9/12 (75%) and 10/12 (83%), respectively.

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 were from a registry maintained by the Hemophilia and Thrombosis Research Society (9 bleeding episodes, 1 surgery). Dosing ranged from 6 to 98 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) 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 (8 non-surgical, 3 surgical and 2 episodes classified as other). Concomitant use of other hemostatic agents occurred in 29/70 (41%); 13 (19%) received more than one hemostatic agent. The most common hemostatic agents used were antifibrinolytics, Factor VIII and activated prothrombin complex concentrates.

The mean 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 programs 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 NovoSeven®, Compassionate Use Programs and HTRS Registry

Outcome ^a	NovoSeven® Dose (micrograms/kg)							Total
	Unknown	<61	61-69	70-80	81-89	90	>90	
Effective N (%)	1 (33)	3 (75)	5 (63)	10 (63)	12 (57)	10 (67)	26 (58)	67
Partial N (%)	1 (33)	0 (0)	0 (0)	3 (19)	3 (14)	2 (13)	11 (24)	20
Ineffective N (%)	0 (0)	1 (25)	3 (38)	2 (13)	2 (10)	2 (13)	7 (16)	17
Unknown N (%)	1 (33)	0 (0)	0 (0)	1 (6)	4 (19)	1 (7)	1 (2)	8
No. of Bleeding Episodes ^c	3	4	8	16	21	15	45	112 ^a

^a Outcome assessed at end of treatment, last observation carried forward.

^b One patient in the HTRS registry was excluded from efficacy analysis since NovoSeven® was used to maintain hemostasis after bleeding had been controlled.

^c N (%) do not add up to 100 due to rounding.

14.4 Glanzmann's Thrombasthenia

Data were collected from the Glanzmann's Thrombasthenia Registry (GTR), the Hemostasis and Thrombosis Research Society (HTRS) registry, and the published literature. The GTR was observational, and therefore not designed to select doses. The GTR captured data for 218 Glanzmann's thrombasthenia patients with 1073 bleeding and surgical events. An independent adjudication committee assessed clinical refractoriness and antibody status based upon historical data from investigators, patterns of treatment, and treatment responses when only platelets were used. Adjudicators defined clinical refractoriness as lack of platelet response. Patients with apparent response to platelets only were not considered refractory, even if coded as such by investigators. Antibody status included GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies. Efficacy was evaluated on a two-point scale (clinical assessment of success or failure of treatment regimen as a whole, blinded and unblinded to investigator coded outcome) in 190 patients with 755 episodes requiring systemic hemostatic therapy (151 patients with 564 severe bleeding episodes, 90 patients with 192 surgeries, one episode was classified as both). Of these a total of 92 patients were treated with NovoSeven® RT for 266 bleeding episodes and 77 patients treated for 160 surgical procedures. A large number of bleeding episodes were treated with NovoSeven® RT alone (109/266 (41%) events).

The median dose of NovoSeven® RT administered for bleeding episodes and surgical procedures was 90 micrograms per kg and the median interval between doses was 3 hours.

For all subjects, concomitant use of other hemostatic agents occurred in 157/266 (59%) bleeding episodes and 94/160 (59%) surgical procedures.

The majority of NovoSeven® RT treated bleeding episodes were in pediatric patients (65%; children and adolescents, 0-16 yrs.).

Of the 266 bleeding episodes treated with NovoSeven® RT, the most common types of bleeding episodes were: epistaxis (116, 43.6%), gum bleeding (48, 18.0%), menorrhagia (36, 13.5%), tooth/dental extraction related (29, 10.9%), and gastrointestinal (23, 8.6%).

Of the patients treated with NovoSeven® RT for surgical procedures, 86% were adults (> 16 years). Major surgery was defined as any invasive operative procedure in which, body cavity was entered, mesenchymal barrier was crossed, facial plane was opened, organ was removed or normal anatomy was operatively altered. Minor surgery was defined as any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue

were manipulated. Surgical procedures treated with NovoSeven® RT included minor (134/160; 83.8%) and major (26/160, 16.3%) procedures. Dental procedures were most common (106, 66.3%), followed by endoscopy (12, 7.5%), nasal procedures (8, 5.0%), excision (7, 4.4%), GI surgery (7, 4.4%) and orthopedic procedures (6, 3.8%). Most surgeries were elective (147, 91.9%), with a few emergency (7, 4.4%) or unspecified (6).

Overall, treatment with NovoSeven® RT was successful in 94.4% of bleeding episodes (Table 9) and 99.4% of surgical procedures (Table 10). Adjudicator-rated efficacy was consistent across treatment regimens, bleed and surgery types, age, and refractory/antibody status. Treatment with NovoSeven® RT was successful in patients with clinical refractoriness with or without platelet-specific antibodies in 94.9% of bleeding episodes and 98.6% of surgical procedures. In patients without refractoriness or platelet-specific antibodies, treatment with NovoSeven® RT was comparable to treatment with platelets.

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

	No. of patients ^c	No. of episodes	Success	Failure	Insufficient data	No Consensus
All NovoSeven®*	92	266	251 (94.4)	4 (1.5)	6 (2.3)	5 (1.9)
By Treatment Regimen						
NovoSeven® only	44	109	101 (92.7)	2 (1.8)	4 (3.7)	2 (1.8)
NovoSeven® ± Platelets ± Other hemostatic agents	69	157	150 (95.5)	2 (1.3)	2 (1.3)	3 (1.9)
By Antibody/Refractory Group						
Refractoriness ± Platelet-specific antibodies ^{a,d}	31	79	75 (94.9)	2 (2.5)	2 (2.5)	0 (0.0)
Platelet-specific-antibodies ^{a,d}	8	10	10 (100.0)	0 (0.0)	0 (0.0)	NA
Neither or unknown ^{b,d}	57	177	166 (93.8)	2 (1.1)	4 (2.3)	5 (2.8)

* All treatment regimens that included treatment with NovoSeven®

^a includes GPIIb/IIIa, 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 episodes with different 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: Adjudicator Evaluation of Efficacy – Surgical Procedures for GTR Data

Treatment group	No. of patients ^c	No. of procedures	Success	Insufficient data ^d
All NovoSeven®*	77	160	159 (99.4)	1 (0.6)
By Treatment Regimen				
NovoSeven® only	35	66	65 (98.5)	1 (1.5)
NovoSeven® ± Platelets ± Other hemostatic agents	57	94	94 (100.0)	0 (0.0)
By Antibody/Refractory Group				
Refractoriness ± Platelet-specific antibodies ^{a,e}	33	70	69 (98.6)	1 (1.4)
Platelet-specific antibodies ^{a,e}	11	24	24 (100.0)	0 (0.0)
Neither or unknown ^{b,e}	36	66	66(100)	0 (0.0)

* All treatment regimens that included treatment with NovoSeven®

^a includes GPIIb/IIIa, 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 episodes with different 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 31/66 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® RT for 23 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

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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:

Presentation	Carton NDC Number	Components
1 mg per vial (1000 micrograms/vial)	NDC 0169 7010 01	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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:

Presentation	Carton NDC Number	Components
1 mg per vial (1000 micrograms/vial)	NDC 0169 7201 01	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

- 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 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.
- Advise patients to follow the recommendations in the FDA-approved patient labeling, regarding proper sharps disposal.

Version: 2017October-V17

NovoSeven® RT is covered by US Patent No. 8,299,029, and other patents pending.

Novo Nordisk® is a registered trademark of Novo Nordisk A/S.

NovoSeven® is a registered trademark of Novo Nordisk Health Care AG.

MixPro® is a registered trademark of Novo Nordisk A/S.

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InVision-Plus®, InVision-Plus CS®, InVision-Plus® Junior® are registered trademarks of RyMed Technologies, Inc.

Bionector® is a registered trademark of Vygon.

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 www.NovoSevenRT.com

Manufactured by:
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 2880 Bagsvaerd, Denmark
 License Number: 1261
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 USA17HDM03364 11/17



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 NOVOSSEVEN® 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.

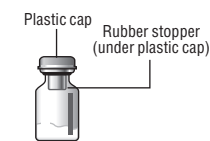
Content

The package contains:

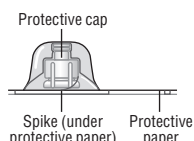
- Vial with NovoSeven® RT powder
- Vial adapter
- Pre-filled syringe with diluent
- Plunger rod (placed under the syringe)

Overview

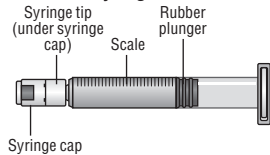
Vial with NovoSeven® RT powder



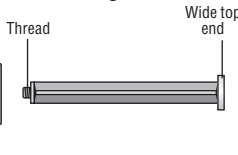
Vial adapter



Pre-filled syringe with diluent



Plunger rod



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.

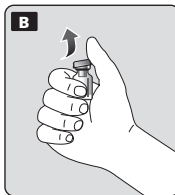
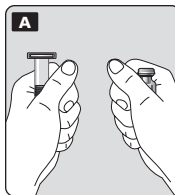
- Wash your hands and dry them properly using a clean towel or air dry.

- 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.**



Don't use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Don't use the equipment if it is expired. Use a new package instead. The expiration date is printed on the outer carton and on the vial, the vial adapter and the pre-filled syringe.

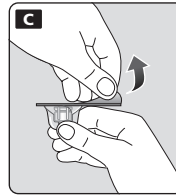
Don't dispose of any of the items until after you have injected the mixed solution.

2. Attach the vial adapter

- Remove the protective paper from the vial adapter.

Don't take the vial adapter out of the protective cap.

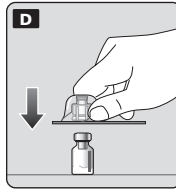
If the protective paper is not fully sealed or if it is broken, don't use the vial adapter.



- 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.**

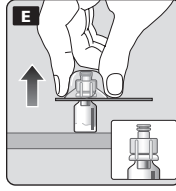
Once attached, don't remove the vial adapter from the vial.



- Lightly squeeze the protective cap with your thumb and index finger as shown.

Remove the protective cap from the vial adapter.

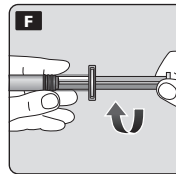
Don't lift the vial adapter from the vial when removing the protective cap.



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.

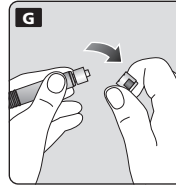
- Immediately connect the plunger rod to the syringe by turning it clockwise into the rubber plunger inside the pre-filled syringe until resistance is felt.



- Remove the syringe cap from the pre-filled syringe by bending it down until the perforation breaks.

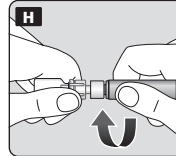
Don't touch the syringe tip under the syringe cap.

If the syringe cap is loose or missing, don't use the pre-filled syringe.



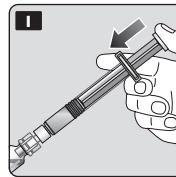
- Screw the pre-filled syringe securely onto the vial adapter until resistance is felt.

⚠ **Avoid touching the sides of the plunger rod at any time.**



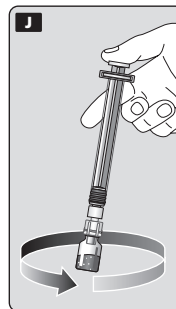
4. Mix the powder with the diluent

- 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.



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.

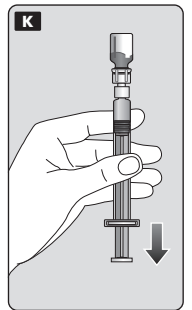
- Turn the syringe with the vial upside down.

- Stop pushing the plunger rod and let it move back on its own while the mixed solution fills the syringe.

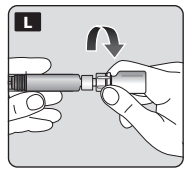
- Pull the plunger rod slightly downwards to draw the mixed solution into the syringe. In case you only need part of the entire dose, use the scale on the syringe to see how much mixed solution you withdraw, as instructed by your doctor or nurse.

- 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.

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.

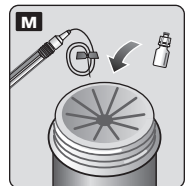
Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or subcutaneous port:

- 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.

The peel-off label found on the NovoSeven® RT vial can be used to record the lot number.

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

For full Prescribing Information please read the other insert included in this package.

Revised: 03/2016

Version: 20160322-v7

NovoSeven® RT is covered by US Patent No. 8,299,029, and other patents pending.

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