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) Room Temperature Stable, Lyophilized Powder
For Intravenous Use Only
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------
How Supplied/Storage and Handling (16) 05/2008

----------INDICATIONS AND USAGE----------
- Treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia (1.1)
- Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia (1.2)
- Treatment of bleeding episodes in congenital FVII deficiency (1.3)
- Prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency (1.4)

----------DOSAGE AND ADMINISTRATION----------
- For intravenous bolus injection only. After reconstitution, administer within 3 hours; do not freeze or store in syringes (2.7)

Hemophilia A or B with Inhibitors – Bleeding Episodes (2.2)
- 90 micrograms/kg bolus injection every 2 hours until hemostasis is achieved
- Post-hemostatic dosing every 3-6 hours for severe bleeds

Hemophilia A or B with Inhibitors – Surgery (2.2)
- 90 micrograms/kg immediately before surgery and every 2 hours during surgery
- Post-surgical dosing: For minor procedures, dosing every 2 hours for 48 hours and then every 2-6 hours, and for major procedures every 2 hours for the first 5 days and then every 4 hours, until healing has occurred

Congenital FVII Deficiency – Bleeding Episodes or Surgery (2.3)
- 15-30 micrograms/kg every 4-6 hours until hemostasis is achieved

Acquired Hemophilia – Bleeding Episodes or Surgery (2.4)
- 70-90 micrograms/kg every 2-3 hours until hemostasis is achieved

----------DOSAGE FORMS AND STRENGTHS----------
- Lyophilized powder in single-use vials: 1.0, 2.0, or 5.0 mg rFVIIa (3)
- After reconstitution with specified volume of histidine diluent, each vial contains 1.0 mg/mL (1000 micrograms/mL) of recombinant FVIIa (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of thrombotic events considered to be low in congenital factor deficiency patients (5.1)
- Increased risk of arterial thromboembolic events observed in elderly patients treated outside the licensed indications (5.2)
- Factor VII deficient patients should be monitored for prothrombin time (PT) and FVII coagulant activity (5.4)
- Administer with caution in patients with known hypersensitivity(5.5)
- Concomitant use with other formulations of NovoSeven is not recommended(5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions are pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema and rash (6.1)

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 rFVIIa and PCCs/aPCCs (7.1)
- NovoSeven RT should not be mixed with infusion solutions (7.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric Use: Safety and effectiveness was not determined to be different across age groups (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NovoSeven® RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable is indicated for:

1.1 Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia

1.2 Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia

1.3 Treatment of bleeding episodes in patients with congenital FVII deficiency

1.4 Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency

NovoSeven RT should be administered to patients only under the supervision of a physician experienced in the treatment of bleeding disorders.

2 DOSAGE AND ADMINISTRATION

2.1 General

NovoSeven RT is intended for intravenous bolus administration only. Evaluation of hemostasis should be used 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.

2.2 Hemophilia A or B with Inhibitors

For bleeding episodes, the recommended dose of NovoSeven RT for hemophilia A or B patients with inhibitors is 90 micrograms/kg given every two hours by bolus infusion until hemostasis is achieved, or until the treatment has been judged to be inadequate. Doses of rFVIIa between 35 and 120 micrograms/kg have been used successfully in clinical trials for hemophilia A or B patients with inhibitors, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved[1]. The minimal effective dose has not been established. 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.

Post-Hemostatic Dosing: The appropriate duration of post-hemostatic dosing has not been studied. For severe bleeds, dosing should continue at 3-6 hour intervals after hemostasis is achieved, to maintain the hemostatic plug. The biological and clinical effects of prolonged elevated levels of Factor VIIa have not been studied; therefore, the duration of post-hemostatic dosing should be minimized, and patients should be appropriately monitored by a physician experienced in the treatment of hemophilia during this time period.

For surgical interventions, an initial dose of 90 micrograms per kg body weight should be given immediately before the intervention and repeated at 2-hour intervals for the duration of the surgery. For minor surgery, post-surgical dosing by bolus injection should occur at 2-hour intervals for the first 48 hours and then at 2- to 6-hour intervals until healing has occurred. For major surgery, post-surgical dosing by bolus injection should occur at 2 hour intervals for 5 days, followed by 4 hour intervals until healing has occurred. Additional bolus doses should be administered if required.

2.3 Congenital Factor VII deficiency

The recommended dose range for treatment of bleeding episodes or for prevention of bleeding in surgical interventions or invasive procedures in congenital Factor VII deficient patients is 15-30 micrograms per kg body weight every 4-6 hours until hemostasis is achieved. Effective treatment has been achieved with doses as low as 10 micrograms/kg. Dose and frequency of injections should be adjusted to each individual. The minimal effective dose has not been determined.

The normal Factor VII plasma concentration is 0.5 micrograms/mL. Factor VII levels of 15-25% (0.075 – 0.125 micrograms/mL) are generally sufficient to achieve normal hemostasis.[2] For example, a 70 kg individual with FVII deficiency (plasma volume of approximately 3000 mL) would thus require 3.2 - 5.4 micrograms/kg of rFVIIa to secure hemostasis, assuming 100% recovery but, since the mean plasma recovery for rFVIIa is 20% for FVII-deficient patients, a rFVIIa dose range of 16-27 micrograms/kg would be required to achieve sufficient FVII plasma levels for hemostasis, which is consistent with the recommended dose range.

2.4 Acquired Hemophilia

The recommended dose range for the treatment of patients with acquired hemophilia is 70-90 micrograms/kg repeated every 2-3 hours until hemostasis is achieved. The minimum effective dose in acquired hemophilia has not been determined. The majority of the effective outcomes were observed with treatment in the recommended dose range. The largest number of treatments with any single dose was 90 micrograms/kg; of the 15 treated, 10 (67%) were effective and 2 (13%) were partially effective.

2.5 Reconstitution

Calculate the NovoSeven RT dosage you will need and select the appropriate NovoSeven RT vial package. The selected package contains 1 vial of NovoSeven RT powder and 1 vial of histidine diluent required to prepare reconstituted NovoSeven RT solution. Reconstitute only with the histidine diluent provided with NovoSeven RT. Do not reconstitute with sterile water or other diluent. Reconstitution should be performed using the following procedures:

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:
   1.0 mg (1000 micrograms) vial + 1.1 mL Histidine diluent
   2.0 mg (2000 micrograms) vial + 2.1 mL Histidine diluent
   5.0 mg (5000 micrograms) vial + 5.2 mL Histidine diluent
   After reconstitution with the specified volume of diluent, each vial contains approximately 1.0 mg/mL NovoSeven RT (1000 micrograms/mL).
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.

2.6 Administration

Administration should take place within 3 hours after reconstitution. Any unused solution should be discarded. Do not freeze reconstituted NovoSeven RT or store it in syringes. NovoSeven RT is intended for intravenous bolus injection only and should not be mixed with infusion solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.

Administration should be performed using the following procedures:

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

3 DOSAGE FORMS AND STRENGTHS

NovoSeven RT is supplied as a white lyophilized powder in single-use vials containing 1.0 mg (1000 micrograms), 2.0 mg (2000 micrograms), or 5.0 mg (5000 micrograms) rFVIIa per vial. 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 is referred to as the histidine diluent. After reconstitution with the histidine diluent, each vial contains approximately 1.0 mg/mL NovoSeven RT (1000 micrograms/mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thrombotic Events within the Licensed Indications

The extent of the risk of thrombotic adverse events after treatment with rFVIIa in patients with hemophilia and inhibitors is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) have an increased risk of developing thrombotic events due to circulating tissue factor (TF) or predisposing coagulopathy. *[See Adverse Reactions (6.1) and Drug Interactions (7.1)]*

Patients who receive NovoSeven RT should be monitored if they develop signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the rFVIIa dosage should be reduced or the treatment stopped, depending on the patient's symptoms.

5.2 Risk of Thromboembolic Events outside the Licensed Indications

The extent of the risk of arterial and venous thromboembolic adverse events after treatment with NovoSeven RT in patients without hemophilia is not known. A clinical study in elderly non-hemophilia intracerebral hemorrhage patients indicated an increased risk of arterial thromboembolic adverse events with use of rFVIIa, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction.[3] Safety and effectiveness has not been established in these settings and the use is not approved by FDA.

5.3 Post-Hemostatic Dosing

Due to limited clinical studies which clearly address the effect of post-hemostatic dosing, precautions should be exercised when NovoSeven RT is used for prolonged dosing. *[See Dosage and Administration (2.2)]*

5.4 Monitoring of Factor VII Deficient Patients for Antibody Formation

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.

5.5 Potential for Hypersensitivity Reactions

NovoSeven RT should be administered with caution 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.

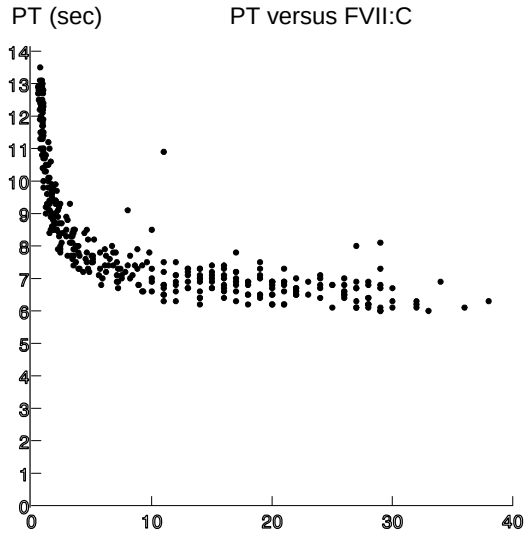
5.6 Concomitant use with Other Formulations

Concomitant use of NovoSeven RT with other formulations of NovoSeven is not recommended due to potential dosing errors based on different concentrations.

5.7 Laboratory Tests

Laboratory coagulation parameters may be used as an adjunct to the clinical evaluation of hemostasis in monitoring the effectiveness and treatment schedule of NovoSeven RT although these parameters have shown no direct correlation to achieving hemostasis. Assays of prothrombin time, activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with rFVIIa 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 U/mL. For FVII:C levels > 5 U/mL, there is no further change in PT.



aPTT: While administration of rFVIIa 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 rFVIIa administration of 35 micrograms/kg and 90 micrograms/kg following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 U/mL for the two dose levels, respectively.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions observed in patients receiving rFVIIa are thrombotic events, however the extent of the risk of thrombotic adverse events after treatment with rFVIIa in individuals with hemophilia and inhibitors is considered to be low. *[See Warnings and Precautions (5.1)]*

The most common adverse reactions observed in clinical studies for all labeled indications of rFVIIa are pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema and rash.

The following sections describe the adverse event profile observed during clinical studies for each of the labeled indications. 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.

Hemophilia A or B Patients with Inhibitors

Two studies (Studies 1 and 2) are described for hemophilia A or B patients with inhibitors treated for bleeding episodes *[See Clinical Studies (14.1)]*. The table below lists adverse events that were reported in ≥2% of the 298 patients with hemophilia A or B with inhibitors that were treated with rFVIIa for 1,939 bleeding episodes. The events listed are considered to be at least possibly related or of unknown relationship to rFVIIa administration.

Body System Event	**# of episodes reported** (n=1,939 treatments)	**# of unique patients** (n=298 patients)
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Hemorrhage NOS	15	8
Fibrinogen plasma decreased	10	5
Skin and Musculoskeletal		
Hemarthrosis	14	8
Cardiovascular		
Hypertension	9	6

Events which were reported in 1% of patients and were considered to be at least possibly or of unknown relationship to rFVIIa administration were: allergic reaction, arthrosis, bradycardia, coagulation disorder, DIC, edema, fibrinolysis increased, headache, hypotension, injection site reaction, pain, pneumonia, prothrombin decreased, pruritus, purpura, rash, renal function abnormal, therapeutic response decreased, and vomiting.

Serious adverse events that were probably or possibly related, or where the relationship to rFVIIa was not specified, occurred in 14 of the 298 patients (4.7%). Six of the 14 patients died of the following conditions: worsening of chronic renal failure, anesthesia complications during proctoscopy, renal failure complicating a retroperitoneal bleed, ruptured abscess leading to sepsis and DIC, pneumonia, and splenic hematoma and gastrointestinal bleeding. Thrombosis was reported in two of the 298 patients with hemophilia.

Surgery Studies

Two clinical trials (Studies 3 and 4) were conducted to evaluate the safety and efficacy of rFVIIa administration during and after surgery in hemophilia A or B patients with inhibitors. *[See Clinical Studies (14.1)]*

In Study 3, six patients experienced serious adverse events: two of these patients had events which were considered probably or possibly related to study medication (acute post-operative hemarthrosis, internal jugular thrombosis). No deaths occurred during the study.

In Study 4, seven of 24 patients had serious adverse events (4 for bolus injection, 3 for continuous infusion). There were 4 serious adverse events which were considered probably or possibly related to rFVIIa treatment (2 events of decreased therapeutic response in each treatment arm). No deaths occurred during the study period.

Congenital Factor VII Deficiency

Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that at least 75 patients with Factor VII deficiency had received rFVIIa - 70 patients for 124 bleeding episodes, surgeries, or prophylaxis regimens; 5 patients in the pharmacokinetics trial.

In the compassionate/emergency use programs, 28 adverse events in 13 patients and 10 serious adverse events in 9 patients were reported. Non-serious adverse events in the compassionate/emergency use programs were single events in one patient, except for fever (3 patients), intracranial hemorrhage (3 patients), and pain (2 patients). The most common serious adverse event in the

compassionate/emergency programs was serious bleeding in critically ill patients. All nine patients with serious adverse events died. One adverse event (localized phlebitis) was reported in the literature. No adverse events were reported in the pharmacokinetics reports or for the HTRS registry. No thromboembolic complications were reported for the 75 patients included here.

Isolated cases of factor VII deficient patients developing antibodies against factor VII were reported after treatment with rFVIIa. These patients had previously been treated with human plasma and/or plasma-derived factor VII. In some cases the antibodies showed inhibitory effect *in vitro*.

Acquired Hemophilia

Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received rFVIIa for 204 bleeding episodes, surgeries and traumatic injuries.

Of these 139 patients, 10 experienced 12 serious adverse events that were of possible, probable, or unknown relationship to treatment with rFVIIa. Thrombotic serious adverse events included cerebral infarction, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Additional serious adverse events included shock and subdural hematoma.

Data collected for mortality in the compassionate use programs, the HTRS registry and the publications spanning a 10 year period, was overall 32/139 (23%). Deaths due to hemorrhage were 10, cardiovascular failure 4, neoplasia 4, unknown causes 4, respiratory failure 3, thrombotic events 2, sepsis 2, arrhythmia 2 and trauma 1.

6.2 Postmarketing Experience

The following post marketing adverse events are reported voluntarily from a population of uncertain size; hence, it is not possible to estimate their frequency or establish a causal relationship to exposure.

The following additional adverse events were reported following the use of rFVIIa in both labeled indications and unlabeled indications that included

individuals with situational coagulopathy and without known coagulopathy: high D-dimer levels and consumptive coagulopathy, thromboembolic events including myocardial infarction, myocardial ischemia, cerebral infarction and/or ischemia, thrombophlebitis, arterial thrombosis, deep vein thrombosis and related pulmonary embolism, and isolated cases of hypersensitivity reactions including anaphylactic reactions. *[See Warnings and Precautions (5.1)]*

Evaluation and interpretation of these post marketing events is confounded by underlying diagnoses, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance. A causal relationship has not been established for the above events.

Additional data on the adverse event profile in general and regarding the frequency of thrombotic events in particular is being collected through a postmarket surveillance program. The Hemophilia and Thrombosis Research Society (HTRS) Registry surveillance program is designed to collect data on all uses of rFVIIa to expand the base of experience regarding the use of rFVIIa.[4] All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355.

7 DRUG INTERACTIONS

7.1 Coagulation Factor Concentrates

The risk of a potential interaction between rFVIIa and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates should be avoided.

7.2 Antifibrinolytic Therapies

Although the specific drug interaction was not studied in a clinical trial, there have been more than 50 episodes of concomitant use of antifibrinolytic therapies (i.e., tranexamic acid, aminocaproic acid) and rFVIIa.

7.3 Infusion Solutions

NovoSeven RT should not be mixed with infusion solutions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Treatment of rats and rabbits with rFVIIa in reproduction studies has been associated with mortality at doses up to 6 mg/kg and 5 mg/kg. At 6 mg/kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg/kg, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg/kg of rFVIIa 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 rFVIIa. There are no adequate and well-controlled studies in pregnant women. NovoSeven RT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

rFVIIa was administered to a FVII deficient patient (25 years of age, 66 kg) during a vaginal delivery (36 micrograms/kg) and during a tubal ligation (90 micrograms/kg). No adverse reactions were reported during labor, vaginal delivery, or the tubal ligation.

8.3 Nursing Mothers

It is not known whether rFVIIa is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of rFVIIa was not determined to be different in various age groups, from infants to adolescents (0 to 16 years of age). Clinical trials were conducted with dosing determined according to body weight and not according to age.

8.5 Geriatric Use

Clinical studies of rFVIIa in congenital factor deficiencies 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 rFVIIa have not been investigated in clinical trials. The following are examples of accidental overdose. One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms/kg and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms/kg to 986 micrograms/kg on five consecutive days. There were no reported complications in either case. A newborn female with congenital factor VII deficiency was administered an overdose of rFVIIa (single dose: 800 micrograms/kg). Following additional administration of rFVIIa and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. A Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms/kg (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke). The recommended dose schedule should not be intentionally increased, even in the case of lack of effect, due to the absence of information on the additional risk that may be incurred.

11 DESCRIPTION

NovoSeven RT is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.[5] NovoSeven RT is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven RT is structurally similar to human plasma-derived Factor VIIa.

The gene for human Factor VII 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.

NovoSeven RT is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials. Each vial of lyophilized drug contains the following:

Contents	1.0 mg Vial	2.0 mg Vial	5.0 mg Vial
rFVIIa	1000 micrograms	2000 micrograms	5000 micrograms
sodium chloride*	2.34 mg	4.68 mg	11.7 mg
calcium chloride dihydrate*	1.47 mg	2.94 mg	7.35 mg
glycylglycine	1.32 mg	2.64 mg	6.60 mg
polysorbate 80	0.07 mg	0.14 mg	0.35 mg
mannitol	25 mg	50 mg	125 mg
Sucrose	10 mg	20 mg	50 mg
Methionine	0.5 mg	1.0 mg	2.5 mg

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

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.

After reconstitution with the appropriate volume of **histidine** diluent, each vial contains approximately 1.0 mg/mL NovoSeven RT (corresponding to 1000 micrograms/mL). The reconstituted vials have a pH of approximately 6.0 in sodium chloride (2.3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), mannitol (25 mg/mL), sucrose (10 mg/mL), methionine (0.5 mg/mL), and histidine (1.6 mg/mL).

The reconstituted product is a clear colorless solution which contains no preservatives. NovoSeven RT 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).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

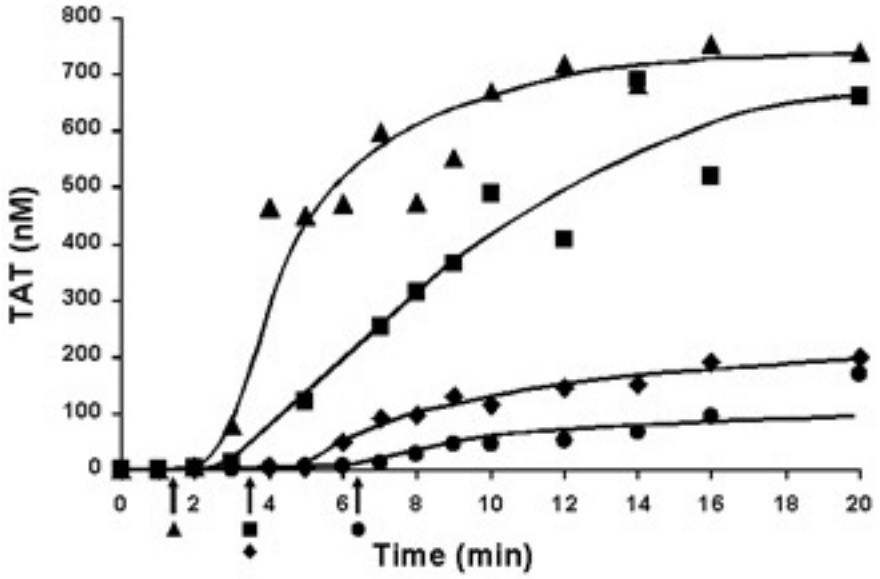
NovoSeven RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic 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)[6], 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.

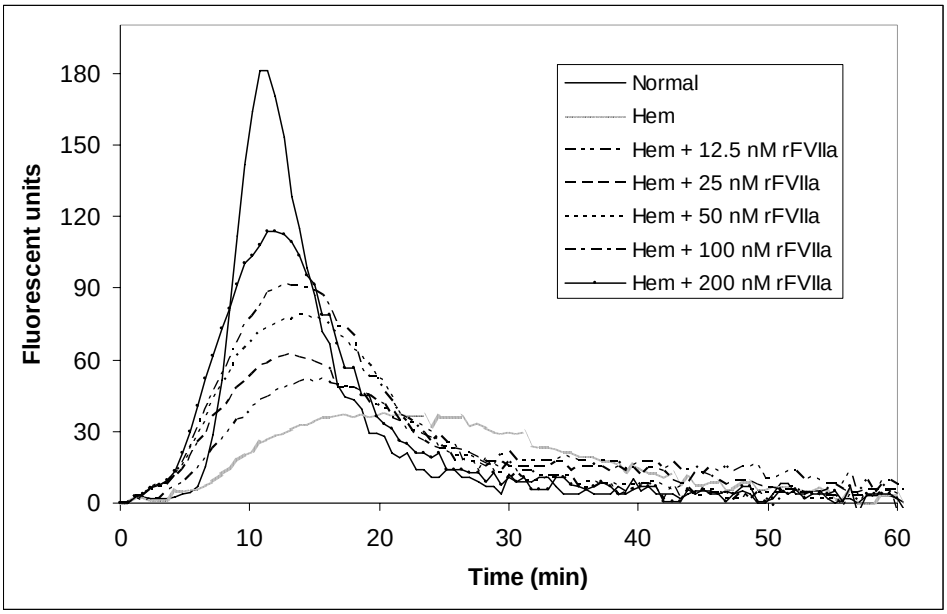
In a separate model, and in line with previous reports[7], escalating doses of rFVIIa in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/microliter. Coagulation was initiated by addition of tissue factor and $CaCl_2$. 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

Hemophilia A or B

Single-dose pharmacokinetics of rFVIIa (17.5, 35, and 70 micrograms/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.[8] Factor VII clotting activities were measured in plasma drawn prior to and during a 24-hour period after rFVIIa administration. The median apparent volume of distribution at steady state was 103 mL/kg (range 78-139). Median clearance was 33 mL/kg/hr (range 27-49). The median residence time was 3.0 hours (range 2.4-3.3), and the $t_{1/2}$ was 2.3 hours (range 1.7-2.7). The median *in vivo* plasma recovery was 44% (30-71%). The products NovoSeven RT and NovoSeven are pharmacokinetically equivalent.[9]

Congenital Factor VII deficiency

Single dose pharmacokinetics of rFVIIa in congenital Factor VII deficiency, 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: total body clearance (70.8-79.1 mL/hr x kg), volume of distribution at steady state (280-290 mL/kg), mean residence time (3.75-3.80 hr), and half-life

(2.82-3.11 hr). The mean *in vivo* plasma recovery was approximately 20% (18.9%-22.2%).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two mutagenicity studies have given no indication of carcinogenic potential for rFVIIa. The clastogenic activity of rFVIIa 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 rFVIIa. Other gene mutation studies have not been performed with rFVIIa (*e.g.*, Ames test). No chronic carcinogenicity studies have been performed with rFVIIa.

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

14 CLINICAL STUDIES

No direct comparisons to other coagulation products have been conducted, therefore no conclusions regarding the comparative safety or efficacy can be made.

14.1 Hemophilia A or B with Inhibitors

Open Protocol Use

The largest number of patients who received rFVIIa during the investigational phase of product development were in an open protocol study (Study 1)[10,11,12] 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. Dose schedules were suggested by Novo Nordisk, but they were subject to the option of the investigator. Clinical outcomes were not reported in a standardized manner. Therefore, the clinical data from Study 1 are problematic for the evaluation of the safety and efficacy of the product by statistical methods.

Dosing Study

Study 2[13] was a double-blind, randomized comparison trial of two dose levels of rFVIIa in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors. Patients received rFVIIa as soon as they could be evaluated in the treatment centers (4 to 18 hours after experiencing a bleed). Thirty-five patients were treated at the 35 micrograms/kg dose (59 joint, 15 muscle and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 micrograms/kg dose (85 joint and 14 muscle bleeding episodes).

Dosing was to be 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/kg groups were: excellent 59% and 60%, effective 12% and 11%, and partially effective 17% and 20%. The average number of injections required to achieve hemostasis was 2.8 and 3.2 for the 35 and 70 micrograms/kg groups, respectively.

One patient in the 35 micrograms/kg group and three in the 70 micrograms/kg group experienced serious adverse events that were not considered related to rFVIIa. Two unrelated deaths occurred; one patient died of AIDS and the other of intracranial hemorrhage secondary to trauma.

Surgery Studies

Two clinical trials (Studies 3 and 4) were conducted to evaluate the safety and efficacy of rFVIIa administration during and after surgery in hemophilia A or B patients with inhibitors.

Study 3 was a randomized, double-blind, parallel group clinical trial (29 patients with hemophilia A or B and inhibitors or acquired inhibitors to FVIII/FIX, undergoing major or minor surgical procedures).[14] Patients received bolus intravenous rFVIIa (either 35 micrograms/kg, N=15; or 90 micrograms/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/kg rFVIIa every 2-6 hours). Efficacy was assessed during the intra-operative period, and post-operatively from the time of wound closure (Hour 0) through Day 5.

When efficacy assessments at each time point were tabulated by a last value carried forward approach (patients who completed the study early having achieved effective hemostasis were counted as "effective" and those who discontinued due to treatment failure or adverse events were counted as "ineffective" at each time point thereafter), the results at the end of the 5-day double-blind treatment period were as summarized in the table below. Twenty-three patients successfully completed the entire study (including the open-label period after the 5-day double blind period) with satisfactory hemostasis.

Study 3: Dose Comparison of Efficacy in Major and Minor Surgery - Last Value Carried Forward*

		Number of effective (E)/ineffective (I) responses in each dose group									
		Major Surgery				**Minor Surgery**					
		35 μg/kg** (n = 5)		**90 μg/kg** (n = 6)		**35 μg/kg** (n = 10)		**90 μg/kg** (n = 8)		**Total** (n = 29)	
		E	**I**	**E**	**I**	**E**	**I**	**E**	**I**	**E**	**I**
Intraoperative		5	0	6	0	10	0	7	1	28	1
Post-Op Hour	0	5	0	6	0	8	2	6	2	25	4
	8	4	1	5	1	9	1	7	1	25	4
	24	4	1	6	0	9	1	6	2	25	4
	48	3	2	6	0	8	2	8	0	25	4
Day	3	2	3	6	0	8	2	8	0	24	5
	4	3	2	6	0	8	2	8	0	25	4
	5	3	2	5	1	8	2	8	0	24	5

* Patients who completed the study early having achieved effective hemostasis were counted as effective at subsequent time-points, and patients who discontinued due to treatment failure or adverse events were counted as ineffective at subsequent time-points. Only effective ratings were counted as successful hemostasis (ratings of "partially effective" were not counted). Ten patients completed the study by Day 5 because their bleeding had resolved and they were discharged from the hospital. Three patients dropped out of the study due to ineffective therapy and 1 patient left the study due to an adverse event.

** μg/kg = micrograms/kg

E: Number of patients where rFVIIa treatment was effective; I: Number of patients where rFVIIa treatment was ineffective

Study 3: 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/kg

Study 4 was an open-label, randomized, parallel trial conducted to compare the safety and efficacy of IV bolus (N=12) and IV continuous infusion (N=12) administration of rFVIIa in hemophilia A or B patients with inhibitors who were undergoing elective major surgery. The types of surgeries that were performed included knee (N=13), hip (N=3), abdomen/lower pelvis (N=2), groin/inguinal area (N=2), circumcision (N=1), eye (N=1), frontal/temporal region of cranium (N=1), and oral cavity (N=1).

Prior to surgery, a 90 micrograms/kg bolus dose of rFVIIa was administered to both bolus and continuous infusion groups. The bolus injection group then received 90 micrograms/kg rFVIIa by IV bolus injection every 2 hours during the procedure and for the first 5 days, then every 4 hours from Day 6 to Day 10. The continuous infusion group received 50 micrograms/kg/h rFVIIa by IV continuous infusion for the first 5 days, and infusion of 25 micrograms/kg/h from Day 6 to Day 10. For both rFVIIa-treated groups, two bolus rescue doses of 90 micrograms/kg were permitted during any 24-hour period.

The bolus injection (90 micrograms/kg) and continuous infusion (50 micrograms/kg/h) treatment groups showed comparable efficacy in achieving and maintaining hemostasis in major surgery from wound closure through Day 10. For the Global Hemostasis Treatment Evaluation for overall success in achieving and maintaining hemostasis at the end of the study period, treatment was rated as being effective in 9 patients (75%) and ineffective in 3 patients (25%) for both treatment groups.

When efficacy assessments at each time point were tabulated by a last value carried forward approach (patients who completed the study early having achieved effective hemostasis were counted as “effective” at each time point, and those who discontinued due to treatment failure counted as “ineffective” at each time point thereafter), the results were as summarized in the table below.

Study 4: Efficacy of Bolus Dosing vs. Continuous Infusion in Major Surgery - Last Value Carried Forward*

		Number of effective (E)/ineffective (I) responses in each dose group			
		Bolus Injection (rFVIIa 90 micrograms/kg) n = 12		**Continuous Infusion (rFVIIa 50 micrograms/kg/h)** n = 12	
		E	**I**	**E**	**I**
Post-Op					
Hour	0	12	0	12	0
	8	12	0	11	1
	24	12	0	10	2
	48	10	2	11	1
	72	9	3	11	1
Day	4	11	1	10	2
	5	11	1	10	2
	6	11	1	10	2
	7	9	3	10	2
	8	10	2	10	2
	9	9	3	10	2
	10	9	3	10	2

* Patients who completed the study early having achieved hemostasis counted as effective at subsequent time-points, and patients who discontinued due to treatment failure counted as ineffective at subsequent time-points. Eight patients completed the study early because their bleeding had resolved and they were discharged from the hospital. Four patients dropped out of the study due to ineffective therapy and 1 patient left the study due to a hemarthrosis that was described as an adverse event.

E: Number of patients where rFVIIa treatment was effective; I: Number of patients where rFVIIa treatment was ineffective

Study 4: Dosing by Treatment Group

	Bolus Injection 90 micrograms/kg (n = 12)	Continuous Infusion 50 micrograms/kg/h (n = 12)
Days of dosing, median (range)	10 (4-15)[a]	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 dosing during the follow-up period after the 10-day study period

14.2 Congenital Factor VII Deficiency

Data were collected from the published literature and internal sources for 70 patients with Factor VII deficiency treated with rFVIIa 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 6-98 micrograms/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 the compassionate use program conducted by Novo Nordisk and the Hemophilia and Thrombosis Research Society (HTRS) registry. A total of 70 patients with acquired hemophilia were treated with rFVIIa 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 compassionate use programs and the HTRS registry were not designed to select doses or compare first-line efficacy or efficacy when used after failure of other hemostatic agents (salvage treatment). A dose response was not seen in doses ranging from 70-90 micrograms/kg.

The mean dose of rFVIIa administered was 90 micrograms/kg (range: 31 to 197 micrograms/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.

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

	rFVIIa Dose (micrograms/kg)							
Outcome[a]	**Un-known**	**<61**	**61-69**	**70-80**	**81-89**	**90**	**>90**	**Total**
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[b]

[a] Outcome assessed at end of treatment, last observation carried forward

[b] One patient in the HTRS registry was excluded from efficacy analysis since rFVIIa was used to maintain hemostasis after bleeding had been controlled.

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

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16 HOW SUPPLIED/STORAGE AND HANDLING

NovoSeven® RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable is supplied as a white, lyophilized powder in single-use vials, one vial per carton. The vials are made of glass, closed with a latex-free, chlorobutyl rubber stopper, and sealed with an aluminum cap. The vials are equipped with a snap-off polypropylene cap. The amount of rFVIIa in milligrams and in micrograms is stated on the label as follows:

1.0 mg per vial (1000 micrograms/vial)	NDC 0169-7010-01
2.0 mg per vial (2000 micrograms/vial)	NDC 0169-7020-01
5.0 mg per vial (5000 micrograms/vial)	NDC 0169-7050-01

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 vials are made of glass closed with a latex-free, chlorobutyl rubber disc, and covered with an aluminum cap. The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Prior to reconstitution, keep refrigerated or store between 2-25°C/36-77°F. Do not freeze. Store protected from light. Do not use past the expiration date.

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

17 PATIENT COUNSELING INFORMATION

Patients receiving NovoSeven RT should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. While bleeding can cause similar symptoms, patients should also be warned 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.

Date of issue: May 9, 2008

Version: 1

License Number: 1261

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