NovoSeven® RT

Coagulation Factor VIIa (Recombinant)
Room Temperature Stable

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

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

——— RECENT MAJOR CHANGES ———

Warnings and Precautions,
Thrombotic Events outside Licensed Indications (5.2) 1/2012

——— 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 (2.6)
- NovoSeven® RT should be administered to patients only under the supervision of a physician experienced in the treatment of bleeding disorders (2.1)

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:
  - Minor surgery – 90 micrograms/kg every 2 hours for 48 hours and then every 2-6 hours, until healing has occurred
  - Major surgery – 90 micrograms/kg 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, 2, 5, or 8 mg rFVIIa (3)
- After reconstitution with specified volume of histidine diluent, each vial contains 1 mg/mL (1000 micrograms/mL) of recombinant FVIIa (3)

——— CONTRAINDICATIONS ———

None (4)

——— WARNINGS AND PRECAUTIONS ———

- Thrombotic events of possible or probable relationship to NovoSeven® occurred in 0.28% of bleeding episodes treated in clinical trials within the approved indications (5.1)
- Increased risk of arterial thromboembolic adverse events with use of NovoSeven® was demonstrated in 2 meta analyses of placebo-controlled clinical trials in populations outside the approved indications (5.2)
- Thrombosis has occurred in women treated with NovoSeven® to control post-partum hemorrhage (5.2)
- Factor VII deficient patients should be monitored for prothrombin time (PT) and FVII coagulant activity, and for antibody formation to NovoSeven® RT (5.4)
- Administer with caution in patients with known hypersensitivity (5.5)

——— ADVERSE REACTIONS ———

In clinical trials, the 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 NovoSeven® RT and PCCs/aPCCs (7.1)
- NovoSeven® RT should not be mixed with infusion solutions (7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

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

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

2.2 Hemophilia A or B with Inhibitors

Treatment of Acute Bleeding Episodes

Hemostatic Dosing

- 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 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 minimum 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.
- Patients should be appropriately monitored by a physician experienced in the treatment of hemophilia during this time period.

Dosing for Surgical Interventions

Minor Surgery

- 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.

Major Surgery

- 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 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 minimum effective dose has not been determined.

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 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

   After reconstitution with the specified volume of diluent, each vial contains approximately 1 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

- NovoSeven® RT is intended for intravenous bolus injection only and should not be mixed with infusion solutions.
- Reconstituted NovoSeven® RT 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 take place within 3 hours after reconstitution.
- Any unused solution should be discarded. Do not freeze reconstituted NovoSeven® RT or store it in syringes.

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 mg (1000 micrograms), 2 mg (2000 micrograms), 5 mg (5000 micrograms), or 8 mg (8000 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 mg/mL NovoSeven® RT (1000 micrograms/mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic Events within the Licensed Indications

Clinical trials within the approved indications revealed that thrombotic events of possible or probable relationship to NovoSeven® occurred in 0.28% of bleeding episodes treated, with the incidence within hemophilia patients with inhibitors to be 0.20%, and in acquired hemophilia an incidence of 4%. Thrombotic events have been identified through postmarketing surveillance following NovoSeven® RT use for each of the approved indications.[2] The incidence of thrombotic events can not be determined from postmarketing data. 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)]*. Caution should be exercised 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.

Patients who receive NovoSeven® RT should be monitored 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, the NovoSeven® RT dosage should be reduced or the treatment stopped, depending on the patient's symptoms.

5.2 Thrombotic Events outside the Licensed Indications

NovoSeven® has been studied in placebo controlled trials outside the approved indications to control bleeding in intracerebral hemorrhage, advanced liver disease, trauma, cardiac surgery, spinal surgery, and other therapeutic areas. Safety and effectiveness has not been established in these settings and the use is not approved by FDA. Two meta analyses of these pooled data indicate an

increased risk of thrombotic events (10.0% in patients treated with NovoSeven® versus 7.5% in placebo-treated patients). Arterial thromboembolic adverse events including myocardial infarction, myocardial ischemia, cerebral infarction and cerebral ischemia were statistically significantly increased with the use of NovoSeven® compared to placebo (5.3 to 5.6% in subjects treated with NovoSeven® versus 2.8 to 3.0% in placebo-treated patients). Other arterial thromboembolic events (such as retinal artery embolism, renal artery thrombosis, arterial thrombosis of limb, intracardiac thrombus, bowel infarction and intestinal infarction) have also been reported.[3,4,5,6,7] While venous thromboembolic events such as deep venous thrombosis, portal vein thrombosis and pulmonary embolism have been reported in clinical trials, the meta analysis of these pooled data from placebo-controlled trials performed outside the currently approved indications did not suggest an increased risk of venous thromboembolic events in patients treated with NovoSeven® versus placebo (4.8% in patients treated with NovoSeven® versus 4.7% in placebo-treated patients).

In spontaneous reports of women without a prior diagnosis of bleeding disorders receiving NovoSeven® for uncontrolled postpartum hemorrhage, thrombotic events were observed. During this period, patients are at increased risk for thrombotic complications.

5.3 Post-Hemostatic Dosing

Precautions should be exercised when NovoSeven® RT is used for prolonged dosing *[See Dosage and Administration (2.2)]*.

5.4 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.

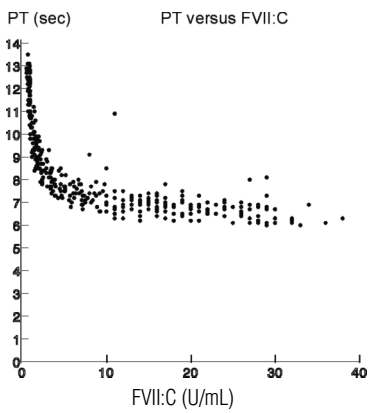
5.5 Hypersensitivity Reactions

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 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 U/mL. For FVII:C levels > 5 U/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/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

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.

6.1 Clinical Trials Experience

Thrombotic events following the administration of NovoSeven® occurred in 0.28% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.20% in clinical trials within the approved indications *[See Warnings and Precautions (5.1)]*.

Adverse reactions observed in clinical trials for all labeled indications of NovoSeven® included pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema, rash (including allergic dermatitis and rash erythematous), pruritus, urticaria, hypersensitivity, cerebral artery occlusion, cerebrovascular accident, pulmonary embolism, deep vein thrombosis, angina pectoris, increased levels of fibrin degradation products, disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and AT-III, thrombosis at i.v. site, non-specified thrombosis, thrombophlebitis, superficial thrombophlebitis.

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

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 NovoSeven® for 1,939 bleeding episodes. The events listed are considered to be at least possibly related or of unknown relationship to NovoSeven® 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 NovoSeven® 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 NovoSeven® 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 NovoSeven® 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 NovoSeven® 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 NovoSeven® — 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.

As with all therapeutic proteins, there is a potential for immunogenicity. Isolated cases of factor VII deficient patients developing antibodies against factor VII were reported after treatment with NovoSeven®. 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*. The incidence of antibody formation is highly 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, 10 experienced 12 serious adverse events that were of possible, probable, or unknown relationship to treatment with NovoSeven®. 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 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.

The following additional adverse events were reported following the use of NovoSeven® in labeled and unlabeled indications that included individuals with and without coagulopathy: high D-dimer levels and consumptive coagulopathy, thrombosis, thrombophlebitis, arterial thrombosis, and thromboembolic events including myocardial ischemia, myocardial infarction, bowel infarction, cerebral ischemia, cerebral infarction, hepatic artery thrombosis, renal artery thrombosis, intracardiac thrombus, portal vein thrombosis, phlebitis, peripheral ischemia, deep vein thrombosis and related pulmonary embolism, injection site pain and isolated cases of hypersensitivity/allergic reactions including anaphylactic shock, flushing, urticaria, rash, and angioedema *[See Warnings and Precautions (5.1)]*.

Fatal and non-fatal thromboembolic events have been reported with use of NovoSeven® when used for off-label or labeled indications.

The Hemophilia and Thrombosis Research Society (HTRS) Registry surveillance program is designed to collect data on the treatment of congenital and acquired bleeding disorders.[8] All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355 or at www.novosevensurveillance.com.

7 DRUG INTERACTIONS

7.1 Coagulation Factor Concentrates

The risk of a potential interaction between NovoSeven® RT 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 Infusion Solutions

NovoSeven® RT should not be mixed with infusion solutions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Treatment of rats and rabbits with NovoSeven® in reproduction studies has been associated with mortality at doses up to 6 mg/kg 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 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®.

8.2 Labor and Delivery

NovoSeven® 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.

There are no adequate and well-controlled studies in labor, delivery, and postpartum periods. In spontaneous reports of women without a prior diagnosis of bleeding disorders receiving NovoSeven® for uncontrolled post-partum hemorrhage, thrombotic events were observed. During this period, patients are at increased risk for thrombotic complications. It is not known to what extent NovoSeven® contributed to the occurrence of these events.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of NovoSeven® 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

There are no adequate and well controlled studies to support the safety or efficacy of using higher than labeled doses in the indicated populations.

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

Congenital Factor VII Deficiency

A newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven® (single dose: 800 micrograms/kg). Following additional administration of NovoSeven® 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).

Hemophilia A or B with Inhibitors

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.

11 DESCRIPTION

NovoSeven® RT is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.[9] 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 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

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 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

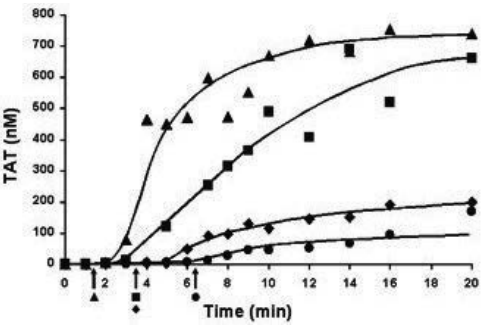
NovoSeven® RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic 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),[10] 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.

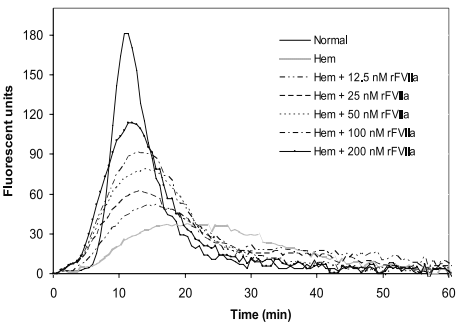
In a separate model, and in line with previous reports,[11] escalating doses of rFVIIa in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/microliter. 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

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/kg NovoSeven®.[12] The pharmacokinetics of rFVII were linear over the dose range of 40 to 180 micrograms/kg. Pharmacokinetics were similar across gender and ethnic groups. Mean steady state volume of distribution ranged from 130 to 165 mL/kg, mean values of clearance ranged from 33 to 37 mL/h x kg, and mean terminal half-life ranged from 3.9 to 6.0 hours.

Hemophilia A or B

Single-dose pharmacokinetics of NovoSeven® (17.5, 35, and 70 micrograms/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.[13] Factor VII clotting activities were measured in plasma drawn prior to and during a 24-hour period after NovoSeven® 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.[14]

In a bolus single-dose pharmacokinetic study, 5 male adults (90 micrograms/kg) and 10 male pediatric (2-12 years) patients (crossover, 90 and 180 micrograms/kg) with severe hemophilia A (10 of 18 subjects had inhibitors) received NovoSeven®.[15] The PK of rFVII following 90 and 180 micrograms/kg IV dose in children indicated dose linearity. Based on the FVII:C assay, the terminal half-life of NovoSeven® was 2.6 hrs in pediatric patients and 3.1 hrs in adults. Based on the 90 microgram/kg dose, the total clearance of NovoSeven® in adults and children was 2767 ± 385 mL/hr (37.6 ± 13.1 mL/hr/kg) and 1375 ± 396 mL/hr (57.3 ± 9.5 mL/hr/kg), respectively. The volume of distribution at steady state (V_{SS}) in adults and children was 121 ± 30 and 153 ± 29 mL/kg, respectively.

Congenital Factor VII deficiency

Single dose pharmacokinetics of NovoSeven® 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%).

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.[16] 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 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/kg would be required to achieve sufficient FVII plasma levels for hemostasis, which is consistent with the recommended dose range.

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/kg/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/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 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®.

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 NovoSeven® during the investigational phase of product development were in an open protocol study (Study 1)[17,18,19] 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[20] was 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. Patients received NovoSeven® 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 NovoSeven®. 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 NovoSeven® 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).[21] Patients received bolus intravenous NovoSeven® (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 NovoSeven® 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 NovoSeven® treatment was effective; I: Number of patients where NovoSeven® 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 NovoSeven® 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 NovoSeven® was administered to both bolus and continuous infusion groups. The bolus injection group then received 90 micrograms/kg NovoSeven® 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 NovoSeven® by IV continuous infusion for the first 5 days, and infusion of 25 micrograms/kg/h from Day 6 to Day 10. For both NovoSeven®-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 (NovoSeven® 90 micrograms/kg) n = 12		Continuous Infusion (NovoSeven® 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 NovoSeven® treatment was effective; I: Number of patients where NovoSeven® 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 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 6-98 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 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 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 NovoSeven® 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 NovoSeven®, Compassionate Use Programs and HTRS Registry

	NovoSeven® Dose (micrograms/kg)							
Outcome[a]	**Unknown**	**<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 NovoSeven® 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 mg per vial (1000 micrograms/vial)	NDC 0169-7010-01
2 mg per vial (2000 micrograms/vial)	NDC 0169-7020-01
5 mg per vial (5000 micrograms/vial)	NDC 0169-7050-01
8 mg per vial (8000 micrograms/vial)	NDC 0169-7040-01

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. 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. Patients should be told to immediately seek medical help if any of the above signs or symptoms occur.

Date of Issue: January 24, 2012

Version: 5

License Number: 1261

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