NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Product Information Form for Hospitals

Indications and Usage

NovoSeven® RT (coagulation Factor VIIa, recombinant) is a coagulation factor indicated for:

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

Important Safety Information

WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

Please see additional Important Safety Information, on page 15.

Please click here for Prescribing Information, including Boxed Warning.

novo nordisk®

Product Information Form for Hospitals

1 AHFS CLASSIFICATION NUMBER

20:28.16

2 GENERIC NAME

Coagulation Factor VIIa, recombinant or Eptacog alfa.

3 SOURCE OF SUPPLY

NovoSeven® RT is manufactured by Novo Nordisk A/S. NovoSeven® RT is distributed by Novo Nordisk Inc.

4 BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

BL 103665, NovoSeven® March 25, 1999 for Congenital hemophilia A or B with inhibitors
BL 103665, NovoSeven® 2005 for Congenital FVII deficiency
BL 103665/5119, NovoSeven® October 13, 2006 for Acquired hemophilia
BL 103665/5231, NovoSeven® RT May 9, 2008 for RT indication
BL 103665, NovoSeven® RT July 7, 2014 for Glanzmann's thrombasthenia

5 PHYSICAL PROPERTIES

a. Macroscopic appearance

NovoSeven® RT is supplied as a room temperature stable, white, lyophilized powder in single-dose vials, one vial per carton. The diluent for reconstitution of NovoSeven® RT is a 10 mmol solution of L-histidine in water and is supplied as a clear colorless solution in either a vial or pre-filled diluent syringe. NovoSeven® RT is available as lyophilized powder in single dose vials of 1, 2, 5, or 8 mg recombinant coagulation factor VIIa (FVIIa).

After reconstitution with the specified volume of diluent, each vial contains approximately 1 mg per mL NovoSeven® RT (1000 micrograms per mL).

b. Solubility

NovoSeven® RT is formulated as a sterile, white lyophilized powder for intravenous injection after reconstitution with the diluent (10 mmol solution of L-histidine in water).

6 CHEMICAL PROPERTIES

a. Structural similarities to other available compounds or groups of compounds

Recombinant coagulation factor VIIa (rFVIIa), the active ingredient in NovoSeven® RT, is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues with an approximate molecular mass of 50 kDa. It is structurally similar to endogenous human coagulation factor VIIa.

b. Recommended storage conditions for NovoSeven® RT

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

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

c. Excipients contained in the commercially available product

The diluent for reconstitution of NovoSeven® RT is a 10 mmol solution of histidine in water for injection and is supplied as a clear colorless solution in a vial or pre-filled diluent syringe. After reconstitution with the appropriate volume of histidine diluent, the product contains the following excipients per vial: 1 mg vial contains 1000 mcg rFVIIa, 2.34 mg sodium chloride*, 1.47 mg calcium chloride dihydrate*, 1.32 mg glycylglycine, 0.07 mg polysorbate 80, 25 mg mannitol, 10 mg Sucrose, 0.5 mg Methionine; 2 mg vial contains 2000 mcg rFVIIa, 4.68 mg sodium chloride*, 2.94 mg calcium chloride dihydrate*, 2.64 mg glycylglycine, 0.14 mg polysorbate 80, 50 mg mannitol, 20 mg Sucrose, 1 mg Methionine; 5 mg vial contains 5000 mcg rFVIIa, 11.7 mg sodium chloride*, 7.35 mg calcium chloride dihydrate*, 6.60 mg glycylglycine, 0.35 mg polysorbate 80, 125 mg mannitol, 50 mg Sucrose, 2.5 mg Methionine; 8 mg vial contains 8000 mcg rFVIIa, 18.72 mg sodium chloride*, 11.76 mg calcium chloride dihydrate*, 10.56 mg glycylglycine, 0.56 mg polysorbate 80, 200 mg mannitol, 80 mg Sucrose, 4 mg Methionine (*per mg of rFVIIa: 0.4 mEq sodium, 0.01 mEq calcium). The reconstituted solution is a clear colorless solution with a pH of approximately 6.0 and contains no preservatives.

7 PHARMACOLOGIC CLASSIFICATION

a. Pharmacologic class

NovoSeven® RT is a hemostatic agent.

b. Mechanism of action

NovoSeven® RT is recombinant factor VIIa when complexed with other coagulation factors can lead to formation of a hemostatic plug and thereby inducing local hemostasis.

c. Pharmacokinetic data

Healthy Subjects

The pharmacokinetics of NovoSeven® was investigated in 35 healthy subjects (17 Caucasian, 18 Japanese, 16 men, 19 women) in a dose-escalation study. Subjects were dosed with 40, 80 and 160 micrograms per kg NovoSeven®. No effect of gender or ethnicity on the pharmacokinetics of NovoSeven® was observed. Range of mean PK parameters across dose groups are shown in Table 1.

The products NovoSeven® and NovoSeven® RT are pharmacokinetically equivalent in a study of 22 patients receiving single doses of both formulations. Mean PK parameters for NovoSeven® RT are shown in Table 1.

Hemophilia A or B

Single dose pharmacokinetics of NovoSeven® (17.5, 35, and 70 micrograms per kg) was studies in 15 subjects with hemophilia A or B in non-bleeding and bleeding states. Median PK parameters for non-bleeding state are shown in Table 1.

In a bolus single-dose pharmacokinetic study, 6 male adults (90 micrograms per kg) and 12 male pediatric (2-12 years) patients (crossover, 90 and 180 micrograms per kg) with severe hemophilia A (10 of 18 subjects had inhibitors to factor VIII) received NovoSeven®. Compared with the adults, body weight normalized clearance of NovoSeven® in children 2-5 years and 6-12 years was higher by 82% and 42%, respectively. Pharmacokinetic parameters for children with Hemophilia are shown in Table 2.

Congenital Factor VII deficiency

Single dose pharmacokinetics of NovoSeven® in 5 patients with severe congenital factor VII deficiency (<1%), at doses of 15 and 30 micrograms per kg body weight, showed no significant difference between the two doses. Mean PK parameters for the two doses are shown in Table 1.

7 Pharmacologic Classification (cont'd)

Table 1: Single Dose Pharmacokinetic Parameters in Healthy Subjects, Patients with Hemophilia A or B, and Patients With FVII Deficiency (Mean (SD))

	Healthy Subjects		Hemophilia A or B		FVII Deficiency
Formulation (n)	rFVIIa (n=35)[a]	rFVIIa (n=22)[b,c]	rFVIIa (n=15)	rFVIIa (n=6)[e]	rFVIIa (n=5)[c]
Ages	20-45	22-44	15-63	30-45	20-43
Doses (mcg/kg)	40, 80, 160	90	17.5, 35, 70	90	30
AUC (h*U/mL)	71.46, 76, 91*	113.26 (17.36)[d]	53.31 (20.27)**	245 (0.73)	23.70 (7.23)[d]
CL (mL/h)	1953-2516	3077 (438)	NA	2767 (385)	NA
CL (mL/h/kg)	33-37	40.43 (6.23)	33.84 (11.72)	37.6 (13.1)	67.7 (17.9)
$t^{1}/_{2}$ (h)	3.9-6.0	3.54 (0.28)	2.72 (0.54)	3.2 (0.3)	2.62 (0.63)
Vss (mL/kg)	130-165	122.96 (20.42)	108.86 (37.15)	121 (30)	230 (70)
MRT (h)	3.66-4.98	3.05 (0.27)	3.33 (0.64)	3.31 (0.38)	3.46 (0.64)
IR ([U/dL]/ [U/kg])	0.89-1.04	1.18 (0.16)[c]	NA	0.94 (0.16)	0.53 (0.2)[c]

*Based upon the 80 mcg/kg dose
**Based upon the 70 mcg/kg dose
NA: Not available
AUC: Area under the curve from time 0 to infinity; CL: Clearance; t½: terminal half-life; Vss: Volume of distribution at steady state: MRT: mean residence time; IR: Incremental recovery; rFVIIa: NovoSeven® original formulation; rFVIIa-25C: NovoSeven® RT
a: Results are for both males and females. The column presents ranges over ethnicity and gender.
b: Study demonstrated bioequivalence of rFVIIa and rFVIIa-25C (NovoSeven® RT)
c: FVIIa assay used: units in IU
d: AUC in h*IU/mL
e: Includes patients with and without inhibitors

7 Pharmacologic Classification (cont'd)

Table 2: Single Dose Pharmacokinetic Parameters in Hemophilia A With and Without Inhibitors (Mean (SD))

Hemophilia A						
Formulation/ Inhibitor status/age group (n)	**rFVIIa, without inhibitors age ≤5 years (n=3)**	**rFVIIa, with inhibitors, age ≤5 years (n=2)**	**rFVIIa, without inhibitors, age 6-12 years (n=3)**	**rFVIIa, with inhibitors, age 6-12 years (n=4)**	**rFVIIa, without inhibitors, Adults (n=2)**	**rFVIIa, with inhibitors, Adults (n=4)**
Age (years)	2-5	4	7-10	7-12	30-32	32-45
Weight (kg)	14-17	22-26	25-38	25-68	72-97	54-89
Doses (mcg/kg)	90, 180	90, 180	90, 180	90, 180	90	90
AUC (h*U/mL)	1.26 (0.09)*	1.51 (0.25)*	1.68 (0.24)*	1.64 (0.31)*	2.92 (0.80)	2.13 (0.62)
CL (mL/h)	1131 (114)	1387 (75)	1878 (499)	1668 (510)	2477 (162)	2960 (378)
CL (mL/h/kg)	73 (8)	61 (9)	55 (7)	52 (12)	30 (8)	43 (15)
$t^{1}/_{2}$ (h)	2.6 (0.9)	1.9 (0.6)	3.0 (1.1)	3.0 (0.5)	3.3 (0.3)	3.2 (0.3)
Vss (mL/kg)	191 (44)	145 (1)	173 (39)	149 (22)	108 (18)	130 (37)
MRT (h)	2.6 (0.5)	2.4 (0.4)	3.1 (0.5)	2.9 (0.3)	3.62 (0.4)	3.09 (0.2)
IR ([U/dL]/ [U/kg])	0.59 (0.06)	0.75 (0.12)	0.75 (0.35)	0.76 (0.20)	1.01 (0.08)	0.89 (0.20)

*Based upon the 90 mcg/kg dose

AUC: Area under the curve from time 0 to infinity; CL: Clearance; t½: terminal half-life; Vss: Volume of distribution at steady state: MRT: mean residence time; IR: Incremental recovery; rFVIIa: (NovoSeven® original formulation)

8 DOSAGE RANGE

a. Dosage range and route of administration

NovoSeven® RT is for intravenous bolus administration only.

- Use hemostasis evaluation to determine the effectiveness of NovoSeven® RT and to provide a basis for modification of the NovoSeven® RT treatment schedule.
- Coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven® RT.

Treatment of Acute Bleeding Episodes

NovoSeven® RT dosing for the treatment of acute bleeding episodes is provided in Table 3 below.

Table 3: Dosing for Treatment of Acute Bleeding Episodes

Dose* and Frequency	Duration of Therapy	Additional Information
Congenital Hemophilia A or B with Inhibitors		
Hemostatic 90 mcg/kg every two hours, adjustable based on severity of bleeding **Post-Hemostatic** 90 mcg/kg every 3-6 hours for severe bleeds	Until hemostasis is achieved, or until the treatment has been judged to be inadequate After hemostasis is achieved to maintain the hemostatic plug	 The appropriate duration of post-hemostatic dosing has not been studied
Acquired Hemophilia		
70-90 mcg/kg every 2-3 hours	Until hemostasis is achieved	
Congenital Factor VII Deficiency		
15-30 mcg/kg every 4-6 hours	Until hemostasis is achieved	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight. Adjust dose and frequency of injections to each individual patient
Glanzmann's Thrombasthenia		
90 mcg/kg every 2-6 hours	In severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved	Platelet transfusions are the primary treatment in patients with Glanzmann's Thrombasthenia without refractoriness to platelets or in patients without platelet-specific antibodies

*The minimum effective dose has not been determined

8 Dosage Range (cont'd)

Congenital Hemophilia A or B with inhibitors

- Dose and administration interval may be adjusted to the individual patient based on the severity of the bleeding.
- For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds. A majority of patients who reported adverse experiences received more than twelve doses. Monitor and minimize the duration of any post-hemostatic dosing.

Perioperative Management

NovoSeven® RT dosing for prevention of bleeding in surgical interventions or invasive procedures (perioperative management) is provided in Table 4 below.

Table 4: Dosing for Perioperative Management

Type of Surgery	Dose and Frequency	Additional Information
Congenital Hemophilia A or B with Inhibitors		
Minor	**Initial**: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery **Post surgical:** 90 mcg/kg every 2 hours for 48 hours then every 2-6 hours until healing occurs	
Major	**Initial**: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery **Post surgical:** 90 mcg/kg every 2 hours for 5 days then every 4 hours or by continuous infusion at 50 mcg/kg/hr until healing occurs	Additional bolus doses can be given
Acquired Hemophilia		
Minor or Major	70-90 mcg/kg immediately before surgery and repeat every 2-3 hours for the duration of the surgery and until hemostasis is achieved*	
Congenital Factor VII Deficiency		
Minor or Major	15-30 mcg/kg immediately before surgery and repeat every 4-6 hours for the duration of the surgery and until hemostasis is achieved* Adjust dose and frequency of injections to each individual patient	Doses as low as 10 micrograms per kg body weight can be effective
Glanzmann's Thrombasthenia		
Minor or Major	**Initial**: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure* **Post surgical:** 90 mcg/kg every 2-6 hours to prevent post-operative bleeding*	Higher doses of 100-140 micrograms per kg can be used for surgical patients who have clinical refractoriness

*The minimum effective dose has not been determined

8 Dosage Range (cont'd)

b. Use in specific populations

Risk Summary

Pregnancy

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

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

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

Risk Summary

Lactation

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

Pediatric Use

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

Hemophilia A or B with Inhibitors

During the investigational phase of product development NovoSeven® was used in 16 children aged 0 to <2 years for 151 bleeding episodes, 27 children aged 2 to <6 years for 140 bleeding episodes, 43 children aged 6 to <12 for 375 bleeding episodes and 30 children aged 12 to 16 years for 446 bleeding episodes.

In a double-blind, randomized comparison trial of two dose levels of NovoSeven® in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors 20 children aged 0 to <12 and 8 children aged 12 to 16 were treated with NovoSeven® in doses of 35 or 70 micrograms per kg dose. Treatment was assessed as effective pain/tenderness as reported by the patient and/or a measurable decrease of the size of the hemorrhage and/or arrest of bleeding within 8 hours [rated as excellent = 51%], within 8-14 hours [rated as effective = 18%] or after 14 hours [rated as partially effective = 25%]) in 94% of the patients.

8 Dosage Range (cont'd)

NovoSeven® was used in two trials in surgery. In a dose comparison 22 children aged 0 to 16 years were treated with NovoSeven®. Effective intraoperative hemostasis (defined as bleeding that had stopped completely or had decreased substantially [rated as effective = 86%] or bleeding that was reduced but continued [rated as partially effective = 9%]) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 10/12 (83%) in the 35 mcg/kg dose group at 48 hours; effective hemostasis was achieved in 10/10 (100%) in the 90 mcg/kg dose group and 9/12 (75%) in the 35 mcg/kg dose group at 5 days. In the surgery trial comparing bolus (BI) and continuous infusion (CI) 6 children aged 10 to 15 years participated, 3 in each group. Both regimens were 100% effective (defined as bleeding has stopped completely, or decreased substantially) intra-operatively, through the first 24 hours and at day 5. At the end of the study period (Postoperative day 10 or discontinuation of therapy) hemostasis in two patients in the BI group was rated effective and hemostasis in one patient was rated as ineffective (defined as bleeding is the same or has worsened). Hemostasis in all three patients in the CI group was rated as effective.

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

Congenital Factor VII deficiency

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

Glanzmann's Thrombasthenia

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

Geriatric Use

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

Please see Important Safety Information, on page 15.
Please click here for Prescribing Information, including Boxed Warning.

9 SAFETY

a. Adverse reactions, toxicities, and special precautions

ADVERSE REACTIONS

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

Clinical trial experience

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

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

Hemophilia A or B Patients with Inhibitors

In two studies for hemophilia A or B patients with inhibitors treated for bleeding episodes (N=298), adverse reactions were reported in ≥2% of the patients that were treated with NovoSeven® for 1,939 bleeding episodes (see Table 5 below).

Table 5: Clinically Relevant Adverse Reactions Reported in ≥2% of the 298 Patients with Hemophilia A or B with Inhibitors

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

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

9 Safety (cont'd)

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

Immunogenicity

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

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

Congenital Factor VII Deficiency

Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that 75 patients with Factor VII deficiency had received NovoSeven®: 70 patients for 124 bleeding episodes, surgeries, or prophylaxis; 5 patients in the pharmacokinetics trial. The following adverse reactions were reported: intracranial hypertension (n=1), IgG antibody against rFVIIa and FVII (n=1), localized phlebitis (n=1).

Immunogenicity

In 75 patients with factor VII deficiency treated with NovoSeven® RT, one patient developed IgG antibody against rFVIIa or FVII. Patients with factor VII deficiency treated with NovoSeven® RT should be monitored for factor VII antibodies.

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

Acquired Hemophilia

Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 patients experienced 8 serious adverse reactions. Serious adverse reactions included shock (n=1), cerebrovascular accident (n=1) and thromboembolic events (n=6) which included cerebral artery occlusion, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions had a fatal outcome.

Please see Important Safety Information, on page 15.
Please click here for Prescribing Information, including Boxed Warning.

Safety (cont'd)

Glanzmann's Thrombasthenia

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

b. Contraindications, Warnings and Precautions

Contraindications

None Known.

Thrombosis

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance.
- Patients with congenital hemophilia receiving concomitant treatment with aPCCs (activated prothrombin complex concentrates), older patients particularly with acquired hemophilia and receiving other hemostatic agents, or patients with a history of cardiac, vascular disease or predisposed to thrombotic events may have an increased risk of developing thrombotic events.
- Monitor patients who receive NovoSeven® RT for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of NovoSeven® RT or stop the treatment, depending on the patient's condition.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, can occur with NovoSeven® RT. Patients with a known hypersensitivity to mouse, hamster, or bovine proteins may be at a higher risk of hypersensitivity reactions. Discontinue infusion and administer appropriate treatment when hypersensitivity reactions occur.

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.

Laboratory Tests

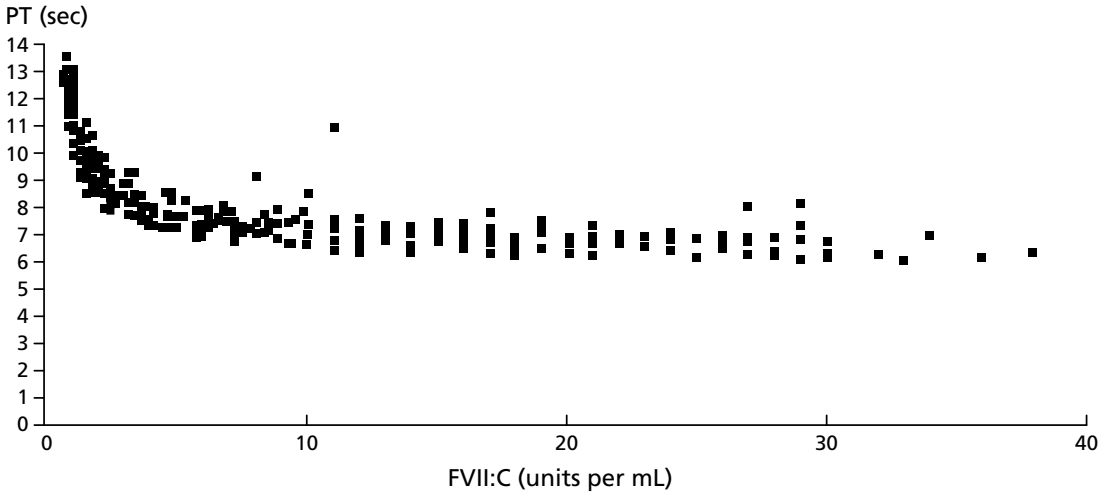
Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment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

Please see Important Safety Information, on page 15.
Please click here for Prescribing Information, including Boxed Warning.

9 Safety (cont'd)

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

PT versus FVII:C



following NovoSeven® RT administration is unknown.

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

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

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

c. List potential drug-drug interactions if deemed clinically significant

- Avoid simultaneous use of activated prothrombin complex concentrates.
- Do not mix NovoSeven® RT with infusion solutions.
- Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII.

10 COMPARISONS

N/A

novo nordisk®

Please see Important Safety Information, on page 15.
Please click here for Prescribing Information, including Boxed Warning.

Indications and Usage

NovoSeven® RT (coagulation Factor VIIa, recombinant) is a coagulation factor indicated for:

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

Important Safety Information

WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

Warnings and Precautions

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance
- Patients with congenital hemophilia receiving concomitant treatment with aPCCs (activated prothrombin complex concentrates), older patients particularly with acquired hemophilia and receiving other hemostatic agents, and patients with a history of cardiac and vascular disease may have an increased risk of developing thrombotic events
- Hypersensitivity reactions, including anaphylaxis, can occur with NovoSeven® RT. Patients with a known hypersensitivity to mouse, hamster, or bovine proteins may be at a higher risk of hypersensitivity reactions. Discontinue infusion and administer appropriate treatment when hypersensitivity reactions occur
- Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity (FVII:C). If FVII:C fails to reach the expected level, or PT 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
- Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis

Adverse Reactions

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

Drug Interactions

- Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII

novo nordisk®

Please click here for Prescribing Information, including Boxed Warning.

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Please see additional Important Safety Information, on page 15.

Please click here for Prescribing Information, including Boxed Warning.

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

NovoSeven® RT
Coagulation Factor VIIa
(Recombinant)