Novo Nordisk®

NovoSeven®
Coagulation Factor VIIa (Recombinant)
For Intravenous Use Only

Rx Only

DESCRIPTION

NovoSeven® is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.[1] NovoSeven is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven 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.

NovoSeven is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials.

Each vial of lyophilized drug contains the following:

Contents	**1.2 mg (60 KIU) Vial**	**2.4 mg (120 KIU) Vial**	**4.8 mg (240 KIU) Vial**
rFVIIa	1200 μg	2400 μg	4800 μg
sodium chloride*	5.84 mg	11.68 mg	23.36 mg
calcium chloride dihydrate*	2.94 mg	5.88 mg	11.76 mg
glycylglycine	2.64 mg	5.28 mg	10.56 mg
polysorbate 80	0.14 mg	0.28 mg	0.56 mg
mannitol	60.0 mg	120.0 mg	240.0 mg

* per mg of rFVIIa: 0.44 mEq sodium, 0.06 mEq calcium

After reconstitution with the appropriate volume of **Sterile Water for Injection, USP (not supplied)**, each vial contains approximately 0.6 mg/mL NovoSeven (corresponding to 600 μg/mL). The reconstituted vials have a pH of approximately 5.5 in sodium chloride (3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), and mannitol (30 mg/mL).

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

CLINICAL PHARMACOLOGY

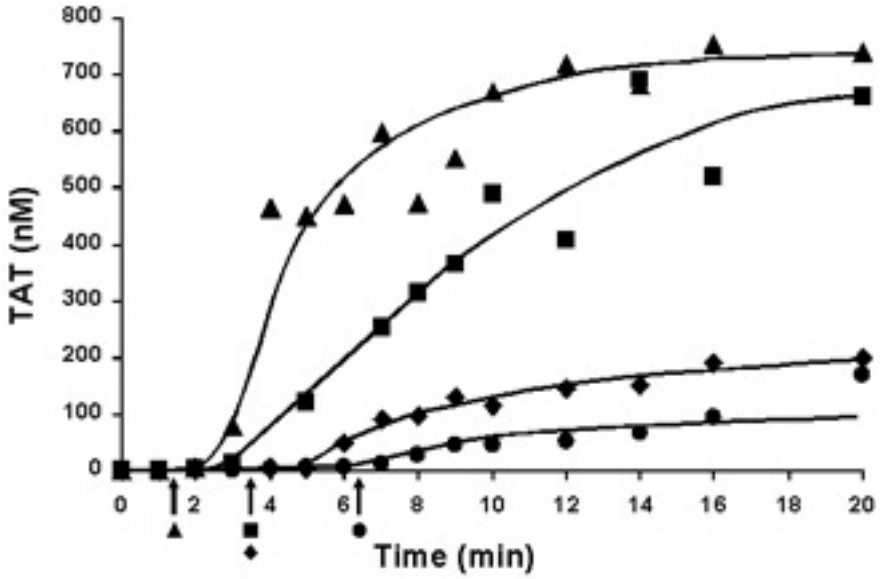
Pharmacodynamics

NovoSeven 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.

The effect of NovoSeven 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)[2], the addition of NovoSeven increased both the rate and level of thrombin generation in normal and hemophilia A blood, with an effect shown at NovoSeven 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 NovoSeven for both types of blood.

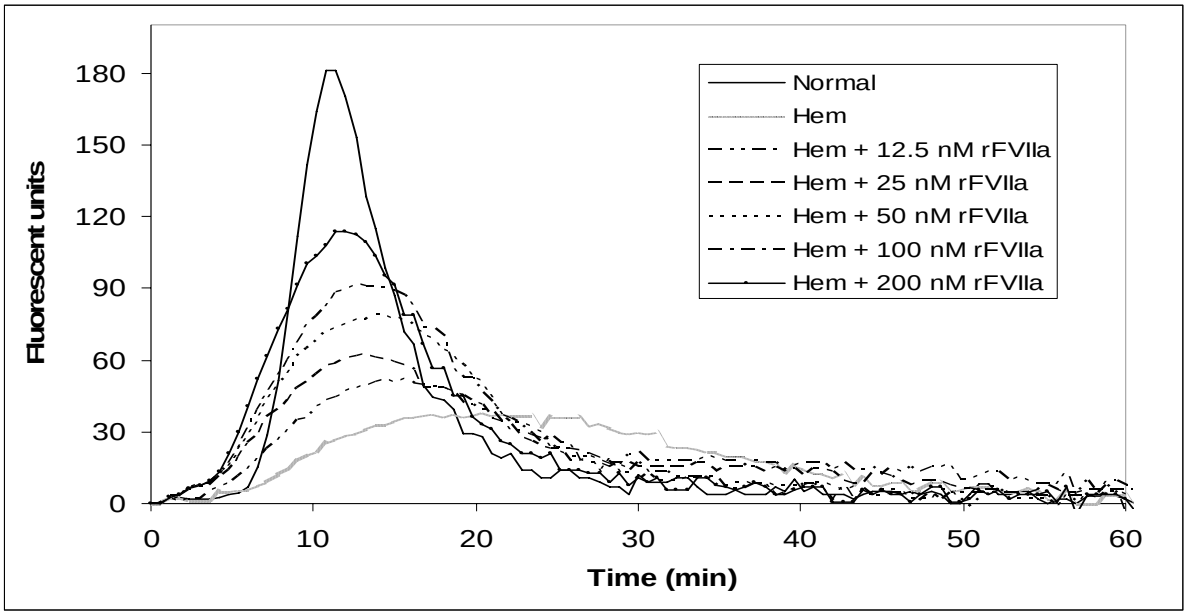
In a separate model, and in line with previous reports[3], escalating doses of NovoSeven in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/μl. 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 TAT 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.

Pharmacokinetics

Hemophilia A or B

Single-dose pharmacokinetics of NovoSeven (17.5, 35, and 70 μg/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.[4] 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%).

Congenital Factor VII deficiency

Single dose pharmacokinetics of NovoSeven in congenital Factor VII deficiency, at doses of 15 and 30 μg 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 μg/mL. Factor VII levels of 15-25% (0.075 – 0.125 μg/mL) are generally sufficient to achieve normal hemostasis.[5] A 70 kg individual with FVII deficiency (plasma volume of approximately 3000 mL) would thus require 3.2 - 5.4 μg/kg of NovoSeven to secure hemostasis, assuming 100% recovery. Since the mean plasma recovery for NovoSeven is 20% for FVII-deficient patients, a NovoSeven dose range of 16-27 μg/kg would be required to achieve sufficient FVII plasma levels for hemostasis.

CLINICAL STUDIES

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

Hemophilia A or B with Inhibitors to Factor VIII or Factor IX

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 A)[6,7,8] 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 A are problematic for the evaluation of the safety and efficacy of the product by statistical methods.

Dosing Study

A double-blind, randomized comparison trial (Study B)[9] of two dose levels of NovoSeven in the treatment of joint, muscle and mucocutaneous hemorrhages was conducted 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 μg/kg dose (59 joint, 15 muscle and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 μg/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 μg/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 μg/kg groups, respectively.

One patient in the 35 μg/kg group and three in the 70 μg/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 C and D) were conducted to evaluate the safety and efficacy of rFVIIa administration during and after surgery in hemophilia A or B patients with inhibitors.

Study C 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).[10] Patients received bolus intravenous rFVIIa (either 35 μg/kg, N=15; or 90 μg/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 µg/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 C: 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.

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

Study C: 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)

Study D was an open-label, randomized, parallel trial conducted to compare the safety and efficacy of i.v. bolus (N=12) and i.v. 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 µg/kg bolus dose of rFVIIa was administered to both bolus and continuous infusion groups. The bolus injection group then received 90 µg/kg rFVIIa by i.v. 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 µg/kg/h rFVIIa by i.v. continuous infusion for the first 5 days, and infusion of 25 µg/kg/h from Day 6 to Day 10. For both rFVIIa-treated groups, two bolus rescue doses of 90 µg/kg were permitted during any 24-hour period.

The bolus injection (90 µg/kg) and continuous infusion (50 µg/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 D: 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 μg/kg) n = 12		**Continuous Infusion (rFVIIa 50 μg/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 D: Dosing by Treatment Group

	Bolus Injection **90 μg/kg** (n = 12)	**Continuous Infusion** **50 μg/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

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 μg/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).

Acquired Hemophilia

Data were collected from four studies in the compassionate use program conducted by Novo Nordisk and the Hemophila 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 μg/kg.

The mean dose of rFVIIa administered was 90 μg/kg (range: 31 to 197 μg/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 µg/kg rFVIIa, Compassionate Use Programs and HTRS Registry

	rFVIIa Dose (µg/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 rFVIIa was used to maintain hemostasis after bleeding had been controlled.

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

INDICATIONS AND USAGE

NovoSeven is indicated for:

- treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia
- 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
- treatment of bleeding episodes in patients with congenital FVII deficiency
- prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency

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

CONTRAINDICATIONS

NovoSeven® Coagulation Factor VIIa (Recombinant) should not be administered to patients with known hypersensitivity to NovoSeven or any of the components of NovoSeven. NovoSeven is contraindicated in patients with known hypersensitivity to mouse, hamster, or bovine proteins.

WARNINGS

The extent of the risk of thrombotic adverse events after treatment with NovoSeven 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) may have an increased risk of developing thrombotic events due to circulating TF or predisposing coagulopathy. (See **ADVERSE REACTIONS** and **Drug Interactions**)

The extent of the risk of arterial and venous thromboembolic adverse events after treatment with NovoSeven in patients without hemophilia is also not known. A clinical study in elderly non-hemophilia intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of NovoSeven, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction.[11]

PRECAUTIONS

General

Patients who receive NovoSeven 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.

Due to limited clinical studies which clearly address the effect of post-hemostatic dosing, precautions should be exercised when NovoSeven is used for prolonged dosing. (See **DOSAGE AND ADMINISTRATION**)

Factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity before and after administration of NovoSeven. 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.

Information for Patients

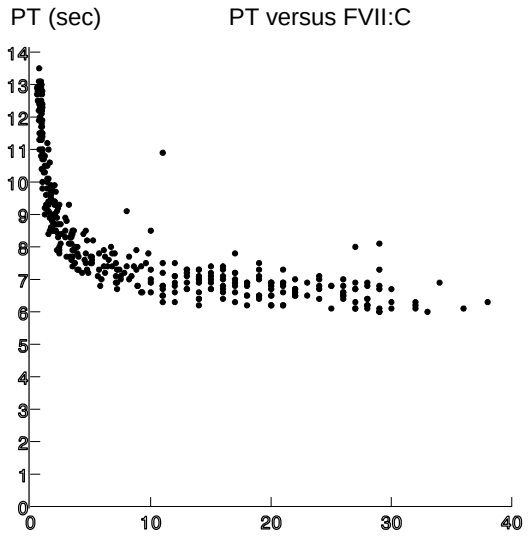
Patients receiving NovoSeven should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions,

including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

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 although these parameters have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT), 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.



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 μg/kg and 90 μg/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.

Drug Interactions

The risk of a potential interaction between NovoSeven 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.

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 NovoSeven.

NovoSeven should not be mixed with infusion solutions until clinical data are available to direct this use.

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 (*e.g.*, Ames test). No chronic carcinogenicity studies have been performed with NovoSeven.

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.

Pregnancy

Pregnancy Category C. 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. There are no adequate and well-

controlled studies in pregnant women. NovoSeven should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

It is not known whether NovoSeven 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.

Pediatric Use

The safety and effectiveness of NovoSeven 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.

Geriatric Use

Clinical studies in hemophilia did not enroll geriatric patients.

ADVERSE REACTIONS

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

The most common adverse reactions observed in clinical studies for all labeled indications of NovoSeven 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

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 GI bleeding. Thrombosis was reported in two of the 298 patients with hemophilia.

Surgery Studies

In Study C, 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 D, 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 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 subjects). 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 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*.

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.

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 NovoSeven 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**)

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 NovoSeven to expand the base of experience regarding the use of NovoSeven.[12] All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355.

OVERDOSAGE

Dose limiting toxicities of NovoSeven® Coagulation Factor VIIa (Recombinant) 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 μg/kg and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 μg/kg to 986 μg/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 μg/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 μg/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.

DOSAGE AND ADMINISTRATION

Dosage

NovoSeven is intended for intravenous bolus administration only. Evaluation of hemostasis should be used to determine the effectiveness of NovoSeven and to provide a basis for modification of the NovoSeven treatment schedule; coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven.

Hemophilia A or B Patients with Inhibitors

For bleeding episodes, the recommended dose of NovoSeven for hemophilia A or B patients with inhibitors is 90 μg/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 μg/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[13]. 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 μg 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 infusion 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 infusion 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.

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 μg per kg body weight every 4-6 hours until hemostasis is achieved. Effective treatment has been achieved with doses as low as 10 μg/kg. Dose and frequency of injections should be adjusted to each individual. The minimal effective dose has not been determined.

Acquired Hemophilia

The recommended dose range for the treatment of patients with acquired hemophilia is 70-90 μg/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 μg/kg; of the 15 treated, 10 (67%) were effective and 2 (13%) were partially effective.

Reconstitution

Reconstitution should be performed using the following procedures:

1. Always use aseptic technique.

2. Bring NovoSeven (white, lyophilized powder) and the specified volume of Sterile Water for Injection, USP, (diluent) to room temperature, but not above 37° C (98.6° F).

   The specified volume of diluent corresponding to the amount of NovoSeven is as follows:

   1.2 mg (1200 μg) vial + 2.2 mL **Sterile Water for Injection, USP**
   2.4 mg (2400 μg) vial + 4.3 mL **Sterile Water for Injection, USP**
   4.8 mg (4800 μg) vial + 8.5 mL **Sterile Water for Injection, USP**

   After reconstitution with the specified volume of diluent, each vial contains approximately 0.6 mg/mL NovoSeven (600 μg/mL).

3. Remove caps from the NovoSeven 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.

5. Insert the needle of the syringe into the sterile water for injection vial. Inject air into the vial and withdraw the quantity required for reconstitution.

6. Insert the syringe needle containing the diluent into the NovoSeven 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 vial does not contain a vacuum).

   Do not inject the diluent directly on the NovoSeven powder.

7. Gently swirl the vial until all the material is dissolved. The reconstituted solution is a clear, colorless solution which may be used up to 3 hours after reconstitution.

Administration

Administration should take place within 3 hours after reconstitution. Any unused solution should be discarded. Do not store reconstituted NovoSeven in syringes. NovoSeven is intended for intravenous bolus injection only and should not be mixed with infusion solutions. As with all parenteral drug products, reconstituted NovoSeven should be inspected visually for particulate matter and discoloration prior to administration. 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. Inject air into the vial and then withdraw the appropriate amount of reconstituted NovoSeven into the syringe.

4. Remove and discard the needle from the syringe; attach a suitable intravenous injection needle and administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.

5. Discard any unused reconstituted NovoSeven after 3 hours.

HOW SUPPLIED

NovoSeven® Coagulation Factor VIIa (Recombinant) is supplied as a white, lyophilized powder in single-use vials, one vial per carton. The vials are made of Class I, Type I, hydrolytic, neutral, white glass, closed with a latex-free, bromobutyl 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:

1.2 mg per vial (1200 μg/vial)	NDC 0169-7060-01
2.4 mg per vial (2400 μg/vial)	NDC 0169-7061-01
4.8 mg per vial (4800 μg/vial)	NDC 0169-7062-01

Storage

Prior to reconstitution, keep refrigerated (2 - 8° C / 36 - 46° F). Avoid exposure to direct sunlight.

Do not use past the expiration date.

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

REFERENCES

1. Roberts, H.R.: Thoughts on the mechanism of action of FVIIa, 2nd Symposium on New Aspects of Hemophilia Treatment, Copenhagen, Denmark, 1991, pgs. 153-156.

2. Butenas, S., et al.: Mechanism of factor VIIa-dependent coagulation in hemophilia blood, Blood 2002; 99: 923-930. Figure A Copyright American Society of Hematology, used with permission.

3. Allen, G.A., et al.: The effect of factor X level on thrombin generation and the procoagulant effect of activated factor VII in a cell-based model of coagulation, Blood Coagulation and Fibrinolysis 2000; 11 (suppl 1): 3-7.

4. Lindley, C.M., et al.: Pharmacokinetics and pharmacodynamics of recombinant Factor VIIa, Clinical Pharmacology & Therapeutics 1994; 55 (6): 638-648.

5. Bauer, K.A.: Treatment of Factor VII deficiency with recombinant Factor VIIa, Haemostasis 1996; 26 (suppl 1): 155-158.

6. Lusher, J., et al.: Clinical experience with recombinant Factor VIIa, Blood Coagulation and Fibrinolysis 1998; 9: 119-128.

7. Bech, M.R.: Recombinant Factor VIIa in Joint and Muscle Bleeding Episodes, Haemostasis 1996; 26 (suppl 1): 135-138.

8. Lusher, J.M.: Recombinant Factor VIIa (NovoSeven®) in the Treatment of Internal Bleeding in Patients with Factor VIII and IX Inhibitors, Haemostasis 1996; 26 (suppl 1): 124-130.

9. Lusher, J.M., et al.: A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with hemophilia A and B, with and without inhibitor, Haemophilia 1998; 4: 790-798.

10. Shapiro A.D., et al: Prospective, Randomised Trial of Two Doses of rFVIIa (NovoSeven) in Haemophilia Patients with Inhibitors Undergoing Surgery, Thrombosis and Haemostasis 1998; 80: 773-778.

11. Mayer, S.A., et al.: Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage, New England Journal of Medicine 2005; 352: 777-785.

12. Parameswaran, R., et al.: Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry, Haemophilia 2005; 11: 100-106.

13. Hedner, U.: Dosing and Monitoring NovoSeven® Treatment, Haemostasis 1996; 26 (suppl 1): 102-108.

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For Information contact:
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540, USA
1-877-NOVO-777
www.novoseven-us.com

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

Novo Nordisk®