NovoSeven®

Coagulation Factor VIIa (Recombinant)
For Intravenous Use 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.

Pharmacokinetics

Single-dose pharmacokinetics of NovoSeven (17.5, 35, and 70 µg/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.[2] 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 $t_{½}$ was 2.3 hours (range 1.7-2.7). The median *in vivo* plasma recovery was 44% (30-71%).

CLINICAL STUDIES

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

Open Protocol Use

The largest number of patients who received NovoSeven during the investigational phase of product development were in an open protocol study[3,4,5] 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 the Open Protocol is problematic for the evaluation of the safety and efficacy of the product by statistical methods. The following two cases describe the extremes of the clinical outcomes that were observed under the Open Protocol:

Case #1: A one-year-old hemophilia B patient had both an inhibitor to Factor IX and would experience severe anaphylactic reactions to any product containing Factor IX. His life threatening hypersensitivity reaction to Factor IX precluded the use of other coagulation products and NovoSeven was requested under the compassionate use program because it contained Factor VIIa and no other coagulation factors. Between the child's ages of one to three, he was successfully treated with NovoSeven for 23 spontaneous joint, muscle, and oral bleeds. NovoSeven was administered by intravenous bolus dosing at 90 µg/kg every two hours. Hemostasis was achieved each time within one to eight days therapy, without reported sequalae. Adverse events were infrequent, minor, and considered unrelated to NovoSeven treatment.

Case #2: A 36-year-old hemophilia A patient with long standing inhibitors experienced pain between his shoulderblades (DAY 0); he treated himself at home for three days with an activated Prothrombin Complex Concentrate (aPCC). From DAY 16-DAY 18, the patient treated himself at home with another aPCC. On DAY 18, he awoke with paraparesis of the lower extremities and was hospitalized. A large epidural hematoma (C6 to T12) was seen on MRI.
The following day (DAY 19), the patient began treatment with NovoSeven, 90 µg/kg every 2 (and later every 3) hours (DAY 19-36). Neurologic and symptomatic improvement was observed. On DAY 29, the NovoSeven dose interval was increased to every four hours. On DAY 31, the patient experienced a massive upper gastrointestinal bleed secondary to stress ulcers (likely dexamethasone induced). He was hypotensive for over two hours, and by the next day, he was requiring large volumes of fluid support and developed abdominal pain. A laparotomy on DAY 32 revealed necrotic large bowel which required resection. Intraoperative and post operative hemostasis was satisfactory on NovoSeven and there was no evidence of thrombosis of the larger mesenteric vessels either at surgery or in the pathologic specimen. On the fourth day post-op (DAY 36), NovoSeven investigational supplies were depleted, and the patient began receiving an aPCC (72 U/kg every 6 hours) and four units of packed red cells per day. During aPCC therapy, bleeding increased; there was coffee ground emesis in the naso-gastric tube. After two days (DAY 38), additional NovoSeven was provided, but the patient was then experiencing severe adult respiratory distress syndrome (ARDS). Within 24 hours of resuming NovoSeven treatment (DAY 40), the patient's life support was voluntarily removed. An autopsy noted the history of bleeding ulcer, ischemic colon, thrombocytopenia, diffuse hemorrhage, lung changes consistent with ARDS, history of epidural hemorrhage, arthropathy, and generalized edema. His stomach had no signs of the ulcers seen the week before on endoscopy indicating healing. On gross neuropathologic exam, his epidural hematoma had resolved.

Dosing Study

A double-blind, randomized comparison trial[6] 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.

INDICATIONS AND USAGE

NovoSeven is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. NovoSeven should be administered to patients only under the direct supervision of a physician experienced in the treatment of hemophilia.

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 is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, or septicemia may have an increased risk of developing thrombotic events due to circulating TF or predisposing coagulopathy. (See **ADVERSE REACTIONS**)
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 Research Society (HRS) Registry surveillance program is designed to collect data on all uses of NovoSeven to expand the base of experience regarding the use of NovoSeven. All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355.

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** section)

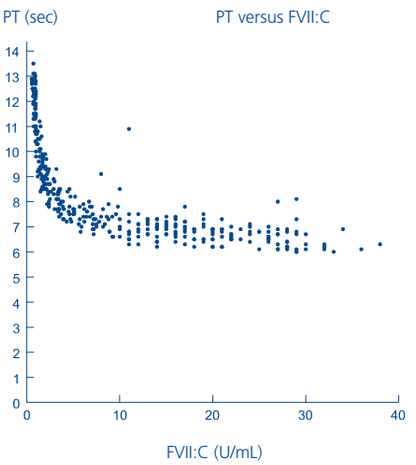
Information for Patients

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. The patients in whom NovoSeven is indicated are male.

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
NovoSeven has been generally well tolerated in clinical studies in 298 patients with hemophilia A or B with inhibitors treated for 1,939 bleeding episodes. The table below lists adverse events that were reported in ≥ 2% of NovoSeven patients and were 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.
In the 298 hemophilia patients, thrombosis was reported in two patients.
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 these 14 patients died of the following conditions: worsening of chronic renal failure, anesthesia complications during proctoscopy, renal failure complicating a retroperitoneal bleed, ruptured absess leading to sepsis and DIC, pneumonia, and splenic hematoma and GI bleeding.

OVERDOSAGE
Dose limiting toxicities of NovoSeven Coagulation Factor VIIa (Recombinant) have not been investigated in clinical trials. Two cases of accidental overdose by bolus administration have occurred in the clinical program. 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. 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. The recommended dose of NovoSeven for hemophilia A or B patients with inhibitors is 90 µg/kg given every two hours 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, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved.[7] 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.

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

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Rx only
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