Summary Basis For Approval

Reference Number: 96-0597

Drug Licensed Name: Coagulation Factor VIIa (Recombinant) (rFVIIa)

Manufacturer: Novo Nordisk Pharmaceuticals Inc.

Trade Name: NovoSeven®

I. Indications for use

NovoSeven®, Coagulation factor VIIa (Recombinant), 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.

II. Dosage form, route of administration and recommended dosage

A. Dosage form and route of administration

NovoSeven® is supplied as a sterile, white lyophilized powder in a single-use vial for injection and is available in nominal dosage strengths of 60 KIU, 120 KIU, and 240 KIU per vial. The units are measured with reference to the first International Standard of FVIIa 89/688. After reconstitution of the lyophilized powder with the appropriate volume of diluent Water for Injection (USP), each vial contains 0.6 mg/ml NovoSeven® (corresponding to 30 KIU/mL), 3 mg/mL sodium chloride, 1.5 mg/mL calcium chloride dihydrate, 1.3 mg/mL glycylglycine, 0.1 mg/mL polysorbate 80, 30 mg/mL mannitol, and has a pH of approximately 5.5.

B. Recommended dosage

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 response 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. 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. The majority of patients who reported adverse experiences received more than twelve doses. The hemostatic response of the patient to treatment with NovoSeven® should provide the basis for establishing and, if necessary, modifying the NovoSeven® treatment schedule; coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven®.

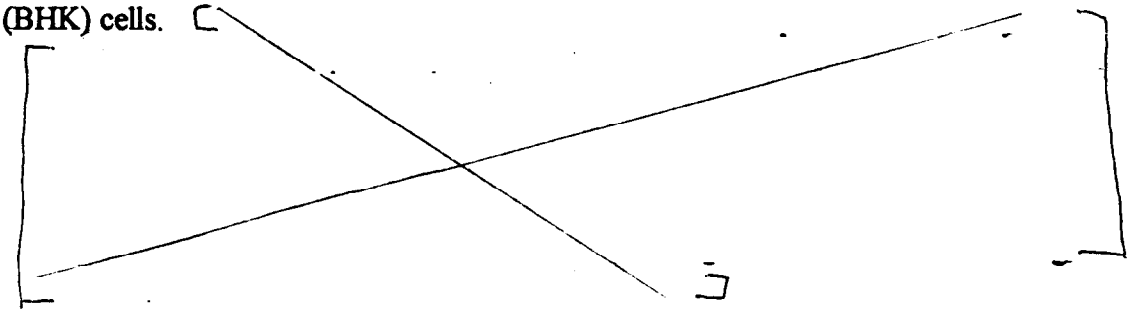
C. Post-hemostatic dosing

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. The 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 treatment of hemophilia during this time period.

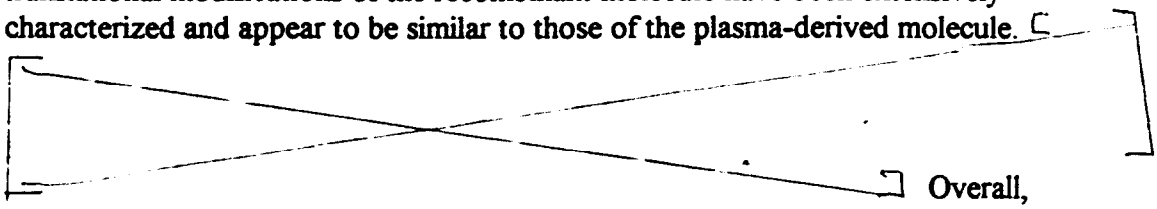
III. Manufacturing and controls

A. Manufacturing

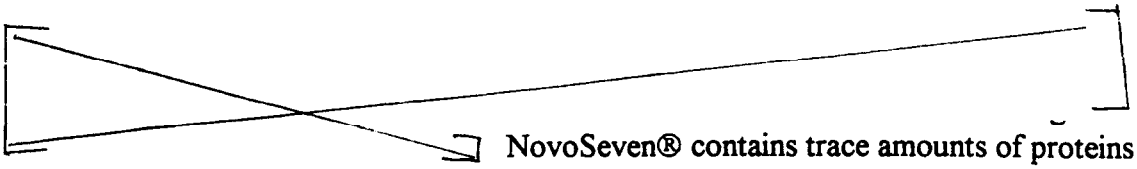
The active ingredient in NovoSeven® is Coagulation Factor VIIa (recombinant) (rFVIIa), a 406-amino acid glycoprotein (MW 50 kDa) that is produced in baby hamster kidney (BHK) cells.



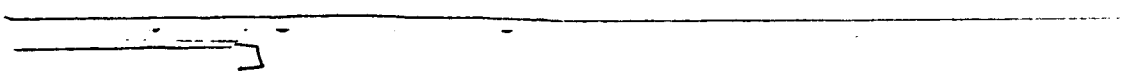
Recombinant FVII is secreted into the culture media in its single-chain form and then proteolytically converted to the active two-chain form, rFVIIa, during a chromatographic purification process. The two-chain activated form is composed of a light chain (N-terminal) of 20 kDa and a heavy chain (C-terminal) of 30 kDa connected by a single disulfide bond. The serine protease activity resides in the heavy chain. The post-translational modifications of the recombinant molecule have been extensively characterized and appear to be similar to those of the plasma-derived molecule.



Overall, NovoSeven® is structurally similar to human plasma-derived factor VIIa. An extensive biochemical and molecular characterization program was performed on NovoSeven®. The study program included the uses of mass spectroscopy, amino acid analysis, tryptic mapping, carbohydrate analysis and circular dichroism spectra, in addition to standard biochemical analyses such as SDS-PAGE, Western blotting, and RP-HPLC.



NovoSeven® contains trace amounts of proteins derived from the manufacturing and purification processes such as murine IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media. In addition,



B. Validation

The manufacturing process for NovoSeven® has been validated for consistency, robustness, and for removal of impurities.

i. Validation of production cell line

The seed stock of the expression vector for factor VII has been developed into the production cell line which has been expanded and cryopreserved as a Master Cell Bank (MCB), from which a Working Cell Bank (WCB) has been established. The MCB, the WCB, and the end-of-production cells have been comprehensively characterized and found to be stable in genotype and free of any detectable bacterial, mycoplasmal, fungal or viral contamination by various assays. However, it can be shown by electron microscopy to contain retrovirus particles, a ubiquitous endogenous viral agent in production cell substrate that has been shown to have no harmful effect and is not known to be infectious.

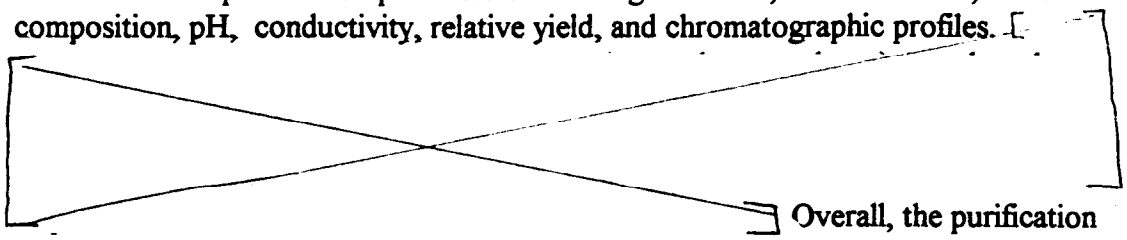
ii. Validation of raw materials

Novo Nordisk has adopted a , that are used in the current manufacturing process.

These tissue culture supplements are subjected to appropriate quality control evaluations before they are accepted for use in manufacturing. Furthermore, these reagents are obtained from countries, e.g. not known to have bovine spongiform encephalopathy (BSE) Acceptance criteria and performance specifications have been established for all materials used in the production process.

iii. Validation of Viral clearance

The purification of NovoSeven® consists of —— chromatographic steps and one detergent ———— treatment step. All —— chromatographic steps in the purification process have been validated for their ability to remove viruses using relevant and appropriate model viruses such as bovine enterovirus (BEV), infectious bovine rhinotracheitis virus (IBR), murine leukemia virus (MuLV), reovirus type 3 (Reo-3), and simian virus 40 (SV40) in acceptable laboratory scale-down studies under GLP (21 CFR 58). Several deviations had occurred during these studies which have no effect on the overall conclusion of the viral inactivation and removal. Process deviations when carrying out these studies are not unexpected. These scale-down studies had been designed to mimic full scale purification parameters including flow rate, residence time, buffer composition, pH, conductivity, relative yield, and chromatographic profiles.



Overall, the purification process has been shown to reduce these viruses by a factor of greater than or equal to 9.4 logs. These study data are summarized in the following table.

Summary of Viral Clearance[a]

Virus	——	——	——	——	Overall
MuLV	4.7	> 6.1	2.4	> 6.3	19.5
Reo-3	7.6	N/A	5.9	> 9.3	22.8
IBR	4.5	> 4.7	5.0	2.9	17.1
BEV	4.8	0.4	3.4	> 8.0	16.2
SV40	3.6	N/A	2.8	> 3.0	9.4

a Log 10 reduction factor.

C. Stability studies

The stability of NovoSeven® has been studied under real-time conditions and stability data were collected for up to 24 months. A documented stability program using relevant analytical test procedures has been used to monitor the integrity of rFVIIa and detect

changes (chemical degradation and physical denaturation) which may occur during storage. Acceptable limits of degradation have been determined from analytical profiles of drug substance lots used in the clinical studies. The stability studies have indicated that the product remains within its specifications throughout its shelf-life of two years. In addition to purity, identity and potency, other product characteristics (including sterility, visual appearance, moisture, pH, degradation products) have been monitored as part of the stability program. Stability data from more than three batches of drug substance that are representative of the manufacturing-scale of production have been reviewed and found to be acceptable.

D. Final container testing

Final product testing studies have indicated that contaminants, such as DNA and host cell proteins are reproducibly removed to acceptable levels in the final drug product. Assays of the drug substance and the final container drug product have been validated for accuracy, precision and reproducibility. Several conformance lots have been submitted to CBER for testing and have been shown to meet the requirements for potency, residual moisture, purity, and sterility. Final container lots have also been shown to conform to requirements for potency and sterility according to 21 CFR Part 610.

E. Establishment inspection

A prelicense inspection of Novo Nordisk A/S's Kalundborg and Gentofte production facilities for Factor VIIa (Recombinant) was conducted by personnel from the Center for Biologics Evaluation and Research and the Office of Regulatory Affairs, November 4-8, 1996. The firm's responses dated December 6, 1996 and February 17, 1997; and the additional information submitted to the Biologics License Application, letters dated September 19, 1997 and April 17, August 25, September 4 and October 2, 1998, which addressed corrective actions taken to correct deficiencies noted on the FDA 483 List of Observations, were reviewed by the inspection team and the review committee. The written statements of corrective actions, which were taken to correct the deficiencies noted during the prelicense inspection, appear to be adequate. A close-out memorandum to this effect dated September 17, 1998, was provided to CBER's Office of Compliance and Biologics Quality, Team Biologics Liaison Staff.

F. Labeling

The package insert, container and package labels are in compliance with 21 CFR §§ 201.57, 610.60, 610.61 and 610.62. The registered trademark, NovoSeven®, is not known to be in conflict with the trademark of any other biological product.

G. Environmental assessment

An environment assessment was filed, reviewed and found to be acceptable. A finding of no significant impact (FONSI) is attached.

IV. Pharmacology

A. Pharmacodynamics

NovoSeven® is a recombinant activated FVII. Factor VII is a vitamin K dependent plasma protein that, when complexed with tissue factor (TF), can activate factor X (FX) to FXa, as well as coagulation factor IX (FIX) to FIXa. Several studies have indicated that FVIIa also possesses FX and FIX catalytic activity in the absence of TF and Ca^{2+} ions. Hemostasis is initiated when FVII or FVIIa complexes with TF at the site of blood vessel injury, and activates factor X to factor Xa, which then converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin, thereby inducing local hemostasis.

B. 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. Factor VII clotting activities were measured in plasma drawn prior to and during a 24-hour period after NovoSeven® administration. NovoSeven® distributed into a volume corresponding to 2 to 3 times the plasma volume. 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 half-life (t1/2) was 2.3 hours (range 1.7-2.7). The median *in vivo* plasma recovery was 44% (30-71%).

V. Clinical experience

A. Open Protocol use

The largest number of patients who received NovoSeven® during the investigational phase of product development were treated under an Open Protocol study 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 emergency

situations. Dose schedules were suggested by Novo Nordisk, but they were subject to the judgement of the investigator. Clinical outcomes were not reported in a standardized manner. Therefore, the clinical data from the Open Protocol were insufficient to evaluate the safety and efficacy of the product by statistical methods.

[redacted]

B. Dosing study

A double-blind, randomized trial was conducted of two doses of NovoSeven® for the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors. Patients received NovoSeven® as soon as they could be evaluated in the treatment centers (4 to 18 hours after experiencing a bleed). Thirty five patients were treated at the 35 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 the 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.

No direct comparisons between NovoSeven® and other coagulation products have been made; therefore, no conclusions regarding the comparative safety or efficacy of NovoSeven® can be made.

VI. Postmarketing clinical study

[redacted]

VII. Postmarketing surveillance

Novo Nordisk has and will continue to conduct a Post Marketing Surveillance (PMS) system to gather further safety data on the use of NovoSeven®. [redacted]

VIII. Blood Products Advisory Committee

On September 26, 1996, presentations by both NNPI representatives and three members of the BLA review committee on the status of the ongoing review of this BLA submission were presented to the BPAC for informational purposes only. Topics such as availability, dosing regimen, safety, statistical considerations, and clinical trial designs were discussed. Manufacturing and control issues were not discussed at this meeting. Various comments on all these issues were made by the BPAC members as well as the general audience. Concerns about the presence of adventitious viruses from the bovine sources and the clinical trial design were expressed. All these concerns were resolved to the satisfaction of the review committee since the BPAC meeting.

IX. Orphan Drug designation

NovoSeven® presently has Orphan Drug status.

LICENSING REVIEW COMMITTEE

Sau C. Cheung 3/24/99
Sau C. Cheung, Ph.D. Date
Chair, BLA Review Committee
HFM-340

Charles M. Maplethorpe 3.24.99
Charles M. Maplethorpe, M.D., Ph.D.
HFM-380 Date

Mark J. Weinstein 3/24/99
Mark J. Weinstein, Ph.D. Date
HFM-340

M. P. Padgett 24-MAR-99
Mary P. Padgett Date
HFM-380

Mary A. Malarkey 3/25/99
Mary A. Malarkey Date
HFM-676

Richard M. Lewis 3.24.99
Richard M. Lewis, Ph.D. Date
HFM-380

Thomas J. Lynch 3/24/99
Thomas J. Lynch, Ph.D. Date
HFM-340

Cornelius J. Lynch Date
HFM-

Martin D. Green Date
HFM-

Donald A. Lebel 3/24/99
Donald A. Lebel Date
HFM-340

Christine Kapfer Date
HFM-340