New Zealand Datasheet

Name of Medicine

NOVOSEVEN® RT
Recombinant Coagulation Factor VIIa (rFVIIa)
eptacog alfa (activated) (bhk)

CAS number: 102786-61-8

Presentation

NOVOSEVEN RT contains activated recombinant coagulation Factor VII of approximate molecular mass 50K Daltons produced by genetic engineering from baby hamster kidney cells (BHK cells). The recombinant coagulation Factor VIIa (rFVIIa) in NOVOSEVEN RT is structurally very similar to human plasma-derived activated Factor VIIa.

NOVOSEVEN RT is supplied as a stable, sterile, freeze-dried white powder in single-use vials. After reconstitution with solvent, each vial contains rFVIIa 1.0 mg/mL (50,000 IU/mL), sodium chloride 2.3 mg/mL, calcium chloride dihydrate 1.5 mg/mL, glycylglycine 1.3 mg/mL, polysorbate 80 0.1 mg/mL and mannitol 25 mg/mL, sucrose 10 mg/mL, methionine 0.5 mg/mL and histidine 1.6 mg/mL.

The units of rFVIIa are international units measured with reference to the first international standard of FVIIa 89/688. These units should not be mistaken for units of other coagulation factors including FVII.

Uses

Actions

The role of FVIIa in the induction of haemostasis includes the direct activation of FIX into FIXa and FX into FXa following the binding of FVIIa to exposed Tissue Factor, initiating the conversion of prothrombin into thrombin Thrombin leads to the activation of platelets and factors V and VIII at the site of injury and the formation of a haemostatic plug by converting fibrinogen into fibrin.

Pharmacological doses of NOVOSEVEN RT activates FX directly on the surface of activated platelets at the local site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independent of tissue factor. Accordingly, the pharmacodynamic effect of FVIIa gives rise to an increased local formation of FXa, thrombin and fibrin.

A theoretical risk for the development of systemic activation of the coagulation system in patients suffering from underlying diseases predisposing them to disseminated intravascular coagulation (DIC) cannot be totally excluded.

Pharmacokinetics

Healthy subjects
The pharmacokinetics of rFVIIa was investigated in 35 healthy Caucasian and Japanese subjects in a dose-escalation study. Subjects were stratified according to gender and ethnic group and dosed with 40, 80 and 160 µg rFVIIa per kg bodyweight and/or placebo (three doses each). The pharmacokinetic profiles indicated dose proportionality. Pharmacokinetics were similar across gender and across ethnic groups. Mean steady state volume of distribution ranged from 130 to 165 ml/kg, mean values of clearance ranged from 33.3 to 37.2 ml/h x kg, and mean terminal half-life ranged from 3.9 to 6.0 hours.

Inhibitors to coagulation Factors VIII or IX
After a single intravenous injection of eptacog alfa (activated) 35-70 μg/kg to haemophiliac A and B patients with inhibitors (n=13), mean peak coagulant activity occurred at 10 minutes and returned to normal at 8-12 hours. The mean Factor VII coagulant half-life was 2.6±0.5 hours.

Using the activated factor VII (FVIIa) activity assay, the pharmacokinetic properties of rFVIIa were studied in 12 paediatric (2-12 years) and five adult patients. Dose proportionality was established in children for the investigated doses of 90 and 180 µg per kg body weight, which is in accordance with previous findings at lower doses (17.5 – 70 µg/kg rFVIIa). Mean clearance was approximately 50% higher in paediatric patients relative to adults (78 versus 53 mL/h x kg), whereas the mean terminal half life was determined as 2.3 hours in both groups. Mean volume of distribution at steady state was 196 ml/kg in paediatric patients versus 159 ml/kg in adults. Clearance appears related to age and bodyweight, therefore in younger patients clearance may be increased by up to 50%.

Factor VII Deficiency
Single dose pharmacokinetics of rFVIIa 15 and 30µg/kg, showed no significant difference between the two doses with regard to dose-independent parameters: total body clearance (70.8 and 79.1 mL/h x kg), volume of distribution at steady state (280-290 mL/kg), mean residence time (3.75-3.80 h), and half-life (2.82-3.11 h). The mean *in vivo* plasma recovery was approximately 20%. Clearance and volume of distribution parameters were increased in Factor VII Deficiency patients compared with other patient populations.

Glanzmann's Thrombasthenia
The pharmacokinetics of rFVIIa in patients with Glanzmann's Thrombasthenia have not been investigated, but is expected to be similar to the pharmacokinetics in haemophilia A and B patients.

Indications
NOVOSEVEN RT is indicated for the control of bleeding and surgical prophylaxis in patients:
- with inhibitors to coagulation Factors VIII or IX;
- with congenital FVII deficiency;
- with Glanzmann's Thrombasthenia, who have antibodies to GPIIb-IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

Dosage and Administration
NOVOSEVEN RT must be reconstituted with the sterile solvent provided and then administered by intravenous bolus injection over a period of 2-5 minutes.

Coagulation parameters should not be used to evaluate NOVOSEVEN RT effectiveness.

Dosing in children
Current clinical experience does not warrant a general differentiation in dosing between children and adults, although children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in paediatric patients to achieve similar plasma concentrations as in adult patients.

Table 1: Dosage Recommendations

Indication	Bolus Injection
Inhibitors to coagulation Factors VIII or IX	**Control of Bleeding:** 35-120 μg/kg every 2-3 hours until control is achieved, then every 3-12 hours if continued treatment is necessary.
	Mild to Moderate Bleeding episodes: Early intervention in patients with Haemophilia A or B with inhibitors has been shown to be efficacious in the treatment of mild to moderate joint, muscle and mucocutaneous bleeds. Based on clinical data two dosing regimens can be recommended: 1) Two to three injections of 90 μg/kg body weight administered at three-hour intervals. 2) One single injection of 270 μg/kg body weight. The duration of the self-administered treatment should not exceed 24 hours. The available data does not support the use of single dose (270 μg/kg) in children < 18 years of age.
	Prophylaxis: Patients with Haemophilia A or B with inhibitors and a high bleeding frequency defined as 4 or more bleeding episodes per month can be treated with NOVOSEVEN RT administered as a once daily dose of 90 μg/kg body weight for up to three months to reduce the frequency of bleeding.
	Surgical Prophylaxis: 35-120 μg/kg every 2-3 hours for 1-2 days, then every 2-6 hours if continued treatment is necessary.
Factor VII deficiency	15-30 μg/kg body weight every 4-6 hours until haemostasis is achieved. Dose and frequency of injections should be individually titrated.
Glanzmann's thrombasthenia	80-120 μg/kg body weight at maximum intervals of 2.5 hours. At least three doses are recommended to secure effective haemostasis. The prophylaxis of invasive/surgical procedures may require a more prolonged use of NOVOSEVEN RT depending on the extent of the procedures.

For patients with Factor IX inhibitors or acquired antibodies to Factor VIII there is no experience of the use of rFVIIa in major surgery.

Reconstitution

Always use aseptic technique. Reconstitute each vial of NOVOSEVEN RT with the specified volume of solvent; avoid forceful impact of solvent on the powder and avoid foaming of the solution by mixing gently. The reconstituted volume contains 1.0 mg/mL rFVIIa (50,000 IU/mL) and appears as a clear colourless solution. The specified volume of solvent required for each corresponding vial of NOVOSEVEN RT is as follows: 1.0 mg vial + 1.1 mL Histidine solvent, 2.0 mg vial + 2.1 mL Histidine solvent, 5.0 mg vial + 5.2 mL Histidine solvent, 8.0 mg vial + 8.1 mL Histidine solvent.

Administration

From a microbiological point of view, the product should be used immediately. If storage is necessary, hold at 2-8°C for not more than 24 hours after reconstitution. Do not store reconstituted NOVOSEVEN RT in syringes – the reconstituted solution should be stored in the vial.

NOVOSEVEN RT is administered by intravenous bolus injection over a period of 2-5 minutes and should not be mixed with infusion solutions or be given in a drip. Do not use NOVOSEVEN RT exhibiting particulates or discoloration. Each vial of NOVOSEVEN RT contains no antimicrobial preservative and is intended for use in one patient on one occasion only. Discard any residue.

Contraindications

NOVOSEVEN RT is contraindicated in patients with:

- hypersensitivity to rFVIIa or any of the components of NOVOSEVEN RT.
- hypersensitivity to mouse, hamster or bovine proteins.

Warnings and Precautions

General

Patients who receive NOVOSEVEN RT should be kept under close observation in case they develop signs and symptoms of untoward activation of the coagulation system or thrombosis. Any findings of this nature indicate that the dosage should be reduced or treatment stopped, depending on the patient's symptoms.

In pathological conditions in which tissue factor may be expressed more extensively than considered normal, there may be a potential risk of development of thrombotic events or induction of Disseminated Intravascular Coagulation (DIC) in association with FVIIa treatment. Such situations may include patients with advanced atherosclerotic disease, crush injury, septicaemia or DIC.

Because of the risk of thromboembolic complications, caution should be exercised when administering NOVOSEVEN RT to patients with a history of coronary heart disease, to patients with liver disease, to patients undergoing and following major surgery, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NOVOSEVEN RT should be weighed against the risk of these complications.

Caution should be exercised in prescribing NOVOSEVEN RT for patients who have significant hypersensitivity to platelets and/or blood products.

As recombinant coagulation factor VIIa contains trace amounts of mouse IgG protein (maximum of 1.2 ng/mg rFVIIa), bovine IgG protein (maximum of 30 ng/mg rFVIIa) and hamster and other bovine proteins (maximum of 19 ng BHK protein/mg rFVIIa), there is a remote possibility that patients treated with NOVOSEVEN RT may develop hypersensitivity to these proteins. In such cases, standard medical treatment should be considered.

If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.

Patients should be informed of the early signs of hypersensitivity reactions. If such symptoms occur, the patient should be advised to discontinue use of the product immediately and contact their physician.

NOVOSEVEN RT should only be administered after guidance from the prescribing physician.

In case of severe bleeds the product should be administered in hospitals preferably specialised in treatment of haemophilia patients with coagulation Factor VIII or IX inhibitors, or if not possible in close collaboration with a physician specialised in haemophilia treatment.

If bleeding is not kept under control, hospital care is mandatory. Patients/carers should inform the physician/supervising hospital at the earliest possible opportunity about all usage of NOVOSEVEN RT.

Factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity before and after administration of NOVOSEVEN RT. In case the factor VIIa activity fails to reach the expected level or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. Thrombosis has been reported in FVII deficient patients receiving FVIIa during surgery but the risk of thrombosis in factor VII deficient patients treated with FVIIa is not well characterised (see Actions, Adverse Effects – Post Marketing Surveillance).

Patients with rare hereditary problems of fructose intolerance, glucose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Carcinogenicity
No chronic carcinogenicity studies have been conducted with rFVIIa.

Concomitant use with Other Formulations
Concomitant use of NOVOSEVEN RT with other formulations of NOVOSEVEN is not recommended due to potential dosing errors based on different concentrations.

Genotoxicity
The clastogenic activity of rFVIIa was evaluated in both *in vitro* studies (cultured human lymphocytes) and *in vivo* studies (mouse micronucleus test). Neither of these studies indicated clastogenic activity of rFVIIa. Gene mutation studies (e.g., Ames test) have not been performed with rFVIIa.

Effects on Fertility
A reproduction study in male and female rats concluded that intravenous administration of rFVIIa at dose levels up to 3.0 mg/kg body weight/day (150,000 IU/kg body weight/day) had no effect upon mating performance, fertility or litter parameters.

Use in the Elderly
Clinical experience with administration of a single dose of 270 µg/kg body weight is limited. Patients with vascular disease may be at increased risk of thrombotic adverse events.

Paediatric Use
Evidence for the safety and effectiveness of rFVIIa has been obtained in the age groups up to adolescence (up to 16 years of age). When dosed on a body weight basis, the efficacy and safety of rFVIIa appear to be comparable in adult and paediatric patients.

No long term studies of the effects of regular use of rFVIIa in children have been performed. The effect of rFVIIa on growth and growth spurts has not been clearly identified.

Use in Pregnancy
Category B1. Teratology studies in rats and rabbits at rFVIIa doses up to 6 and 5 mg/kg/day IV, respectively, showed no adverse effects on litter parameters and fetuses. The rat and rabbit doses of 6 and 5mg/kg/day, respectively, corresponds to approximately 2.5 and 1.8 times the estimated human exposure at the maximum recommended therapeutic dose, based on AUC.

As a precautionary measure it is preferable to avoid the use of rFVIIa during pregnancy. Data on a limited number of exposed pregnancies within approved indications indicate no adverse effects of rFVIIa on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available and there are no adequate or well-controlled studies in pregnant women. rFVIIa should only be given in pregnancy if clearly needed.

Use in Lactation
It is not known whether rFVIIa is excreted in human breast milk but since many drugs are caution should be exercised when rFVIIa is administered to lactating women.

The excretion of rFVIIa in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with rFVIIa should be made taking into account the benefit of breast-feeding to the child and the benefit of rFVIIa therapy to the mother.

Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

Adverse Effects

rFVIIa has been generally well tolerated in clinical studies. Table 2 provides the frequencies of serious and non-serious adverse drug reactions, listed by system organ class, from clinical trials conducted in 484 patients (including 4297 treatment episodes) with haemophilia A and B, acquired haemophilia, factor VII deficiency and Glanzmann's thrombasthenia.

Table 2: Frequency of adverse drug reactions by system organ class

Blood and the lymphatic system disorders	
Rare (≥1/10,000, <1/1,000)	- Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of anti-thrombin (AT) - Coagulopathy
Gastrointestinal disorders	
Rare (≥1/10,000, <1/1,000)	Nausea
General disorders and administration site conditions	
Uncommon (≥ 1/1,000, <1/100)	-Therapeutic response decreased. It is important that the dosage regimen of NOVOSEVEN RT is compliant with the recommended dosage as described under 'Dosage and Administration' -Pyrexia
Rare (≥1/10,000, <1/1,000)	- Injection site reaction including injection site pain
Immune system disorders	
Rare (≥1/10,000, <1/1,000)	- Hypersensitivity
Investigations	
Rare (≥1/10,000, <1/1,000)	- Increased fibrin degradation products - Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
Nervous system disorders	
Rare (≥ 1/10,000, <1/1,000)	- Headache
Skin and subcutaneous tissue disorders	
Uncommon (≥1/1,000, <1/100)	- Rash (including allergic dermatitis and rash erythematous) - Pruritus and urticaria

Vascular disorders	
Rare (≥ 1/10,000, <1/1,000)	- Arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia.
Uncommon (≥ 1/1000, <1/100)	- Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia,)
Rare (≥ 1/10,000, <1/1,000)	- Angina pectoris
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.	

Anaphylaxis, flushing, angioedema and intracardiac thrombus have been reported post-marketing only (i.e. not in clinical trials) but with an unknown frequency.

Patients with acquired haemophilia
During clinical trials conducted in 61 patients with acquired haemophilia with a total of 100 treatment episodes, the following adverse drug reactions were reported with a frequency of common (≥1/100 to <1/10): Specific arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), specific venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products

Inhibitory antibody formation
In post-marketing and clinical experience, there have been no confirmed reports of inhibitory antibodies against NOVOSEVEN RT or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven has been reported in a post-marketing observational registry of patients with congenital FVII deficiency.

In clinical trials of patients with factor VII deficiency, formation of antibodies against NOVOSEVEN RT and FVII is the only adverse drug reaction reported (frequency: common (≥1/100 to <1/10)). In some cases, the antibodies showed inhibitory effect *in vitro*. Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived factor VII, severe mutation of FVII gene, and overdose of NOVOSEVEN RT, were present. Patients with factor VII deficiency treated with NOVOSEVEN RT should be monitored for factor VII antibodies (see Warnings and Precautions).

Thromboembolic events outside approved indications
When NOVOSEVEN RT is administered to patients outside approved indications, arterial thromboembolic events are common (≥ 1/100 to <1/10). A higher risk of arterial thromboembolic adverse events (see Table 2 – 'Vascular disorders 5.3% in patients treated with NOVOSEVEN RT versus 2.8% in placebo-treated patients) has been shown in a meta-analysis of pooled data from placebo-controlled trials conducted outside current approved indications in various clinical settings, each of these having distinct patient characteristics and hence different underlying risk profiles.

Thromboembolic events may lead to cardiac arrest.

Safety and efficacy of NOVOSEVEN RT have not been established outside the approved indications and therefore NOVOSEVEN RT is not recommended.

Post Marketing Surveillance
In an observational registry (F7HAEM-3578) covering subjects with congenital FVII deficiency, 3 out of 91 surgical patients experienced thromboembolic events.

Interactions

The risk of a potential interaction between NOVOSEVEN RT and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not should be avoided.

Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is however limited.

There are no clinical data available on interaction between rFVIIa and rFXIII. Based on a non-clinical study it is not recommended to combine rFVIIa and rFXIII. A potential synergistic effect of combined treatment with rFXIII and rFVIIa in an advanced cardiovascular model in the cynomolgus monkey resulted in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds.

Effects on Laboratory Tests

The relationship between the prothrombin time (PT), activated partial thromboplastin time (aPTT) and levels of the plasma FVII clotting activity (FVII:C) has been investigated in one core laboratory. *The therapeutic range has not been identified for any of the assays.* Therefore coagulation parameters should be used only as an adjunct to the evaluation of clinical haemostasis to monitor the effectiveness and treatment schedule of NOVOSEVEN RT in patients.

FVII:C was measured in a one step coagulation system containing FVII-deficient plasma (immunodepleted, Novo Nordisk A/S) and rabbit brain thromboplastin (type C, Manchester Comparative Reagents Ltd., UK). Coagulation was started by adding thromboplastin and Ca++. Pooled citrated plasma from healthy normal subjects was used as calibrator and was assigned an arbitrary potency of 1U/mL.

The prothrombin time (PT) shortens to 7 seconds and seems to reach a plateau at plasma FVII:C levels of approximately 5 U/mL. Data indicate that a clinical improvement is associated with a shortening of the PT of 3 - 4 seconds from baseline, and that this shortening is maintained throughout the treatment with therapeutic doses. The PT cannot be used to differentiate plasma FVII:C levels > 5 U/mL. The PT assay is performed according to the instructions given in the kit “IL Test™ PT-Fibrinogen: Calcium thromboplastin for the simultaneous *in vitro* determination of Prothrombin Time (PT) and Fibrinogen in plasma” from Instrumentation Laboratory. Note that penicillins cause a reduction in prothrombin time.

Although administration of rFVIIa shortens the aPTT, normalisation is usually not observed in doses shown to induce clinical improvement. Experience so far indicates that a shortening of 15 - 20 seconds was associated with clinical improvement. It is not known if aPTT is helpful in the monitoring of treatment. The aPTT assay is performed according to the instructions given in the kit “IL Test™ APTT-Micronized Silica: Cephalin with micronized

silica for the *in vitro* determination of activated partial thromboplastin time (APTT) in plasma" from Instrumentation Laboratory.

For all the assays different thromboplastins may give different results.

In patients with a severe FVII-deficiency, replacement therapy with rFVIIa in doses of 15 to 30 μg/kg at 4-6 hour intervals has been shown to significantly shorten or normalise prothrombin time.

Overdosage

Dose limiting toxicities of NOVOSEVEN RT have not been investigated in clinical trials

A few cases of overdose have been reported in patients with haemophilia. The only complication reported in connection with an overdose was a slight transient increase in blood pressure in a 16 year-old patient receiving 24 mg rFVIIa instead of 5.5 mg.

No cases of overdose have been reported in patients with acquired haemophilia or Glanzmann's thrombasthenia.

In patients with factor VII deficiency, where the recommended dose is 15-30 μg/kg rFVIIa, one episode of overdose has been associated with a thrombotic event (occipital stroke) in an elderly (>80 years) male patient treated with 10-20 times the recommended dose. In addition, the development of antibodies against NOVOSEVEN and FVII has been associated with overdose in one patient with factor VII deficiency.

The dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred.

For further information on overdose contact the Poisons Information Centre on 0800 764766.

Pharmaceutical Precautions

Store below 25°C. Protect from light. Do not freeze to prevent damage to the solvent vial/pre-filled syringe. Do not use after the expiry date. To reduce the microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2ºC to 8ºC for not more than 24 hours. The reconstituted solution should be stored in the vial.

Medicine Classification

General Sale Medicine.

Package Quantities

The NOVOSEVEN pack contains a single use glass vial of 1.0 mg (50,000 IU), or 2.0 mg (100,000 IU), or 5.0 mg (250,000 IU), or 8.0 mg (400,000 IU), white, lyophilised powder (NOVOSEVEN RT) and either:

a solvent vial.

or

a pre-filled syringe containing solvent, and
a plunger rod, and
a vial adapter.

The powder vials are closed with a latex-free, chlorobutyl rubber stopper, and sealed with an aluminium cap. The vials are equipped with a snap-off polypropylene cap.

The diluent for reconstitution of NOVOSEVEN RT is a 10 mmol solution of histidine in water for injection, is supplied as a clear colourless solution, and is referred to either as the solvent vial or as the pre-filled syringe. The vials are made of glass closed with a chlorobutyl rubber disc, and covered with an aluminium cap. The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene. The pre-filled syringe is made of a type I glass barrel with a polypropylene backstop and bromobutyl rubber plunger. The syringe cap consists of a bromobutyl rubber and polypropylene tamper evident seal. The plunger rod is made of polypropylene.

Further Information

Incompatibilities

NOVOSEVEN RT is intended for intravenous bolus injection only and should not be mixed with infusion solutions or be given in a drip.

List of Excipients

Powder
Sodium chloride
Calcium chloride dihydrate
Glycylglycine
Polysorbate 80
Mannitol
Sucrose
Methionine
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

Solvent
Histidine
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Water for injections

Clinical Trials

Inhibitors to coagulation Factors VIII or IX

Data from five clinical studies of rFVIIa for control of bleeding in patients with inhibitors to coagulation Factors VIII and IX are listed in Table 3. None of the studies used an active or placebo control. All patients were male, with an age range of 1-81 years. Eighty six percent of patients had inhibitors.

Table 3: Clinical trials of rFVIIa
Control of bleeding in patients with inhibitors to coagulation Factors VIII and IX

Study	Bleeding indication	No. Pts (bleeds)	Dose μg/kg	Schedule	No. Treatments	Effectiveness % bleeds controlled	
01	Surgery	10 (10)	35-90	q2h 0-48h then q2-6h	24-196 (3-20 days)	70	
03	Limb/life threat	9 (11)	90-120	q2h until improved, then q3-12h	(5-33 days)	91	
						Joint	***Muscle***
02	Joint or muscle	44 (96)	90	q3h (≤4 doses)	2.0 (av)	91	94
04	Joint or muscle	35 (82) 43 (109)	35 70	q2.5h (6 doses)	2.8 (av) 3.2 (av)	71 71	53 71
05	Joint or	6 (13)	35	q3-4h	6.5 (av)	55	-

	muscle	10 (20)	70		4.7 (av)	47	50

Studies 04 and 05 were randomised dose comparisons of 35 and 70 μg/kg. Neither study found a statistically significant difference between dose levels.

Efficacy and Safety of Single-dose Regimen of rFVIIa in mild to moderate bleeding
The efficacy and safety of a single 270 µg/kg dose of rFVIIa for the treatment of bleeding episodes in haemophilia patients with inhibitors was studied in two randomised, double blind trials (F7HAEM-1510 and F&HAEM-2068) which compared the 270 µg/kg regimen with a standard regimen of 3 doses of 90 µg/kg at 3-hourly intervals. Subjects assessed the efficacy of treatment according to changes in joint pain and mobility over the 9 hours from initiation of treatment. The global response was assessed as either a success or failure. Results are summarised in the following table:

Table 4: Summary of Results by Age Groups for studies F7HAEM-1510 and F7HAEM-2068

	F7HAEM-1510		**F7HAEM-2068**		**Combined**	
rFVIIa(µg/kg)	270	3 × 90	270	3 × 90	270	3 × 90
Total Patients treated, n	20	20	22	21	42	41
Response, n (%)						
Global Response success[(A)]	13(65)	14(70)	8(36)	12(57)	21(50)	26(63)
Need for additional haemostatic agents	2(10)[(B)]	3(15)[(B)]	10(45)[(C)]	10(48)[(C)]	12(29)	13(32)
Adult patients treated (≥ 18 yrs), n	16	16	9	8	25	24
Response, n (%)						
Global response success[(A)]	10(63)	10(63)	5(56)	5(63)	15(60)	15(63)
Need for additional haemostatic agents	2(13)	3(19)	1(11)	3(38)	3(12)	6(25)
Child/adolescent patients treated (< 18 years), n	4	4	13	13	17	17
Response n (%)						
Global Response success[(A)]	3(75)	4(100)	3(23)	7(54)	6(35)	11(65)
Need for additional haemostatic agents	0(0)	0(0)	9(69)	7(54)	9(53)	7(41)
(A) as defined by the Global Treatment Response, (B) within 48 hours, (C) within 2 days						

The 270 µg/kg dose was shown to have comparable efficacy to the standard dose regimen in adults. However, in children comparable efficacy could not be concluded. The single dose regimen was not associated with any increase in toxicity.

Efficacy and Safety of Prophylactic Use of rFVIIa
The efficacy and safety of a secondary prophylaxis regimen of rFVIIa was demonstrated in a single, double blind, uncontrolled trial (study F7HAEM-1505). The study enrolled subjects with a history of frequent bleeds (>4 episodes per month). Subjects were followed for an initial 3-month treatment period to establish frequency of bleeding, and were then treated with rFVIIa daily for the next 3-month period. Treatment with rFVIIa 90 µg/kg once daily resulted in a 45% reduction in bleeding frequency. Median frequency of bleeding decreased from 5.4 per month during the initial observation period to 2.8 per month for the treatment period ($p<0.001$). In a further 3-month follow-up period without treatment the median bleeding frequency (3.9 per month) was 27% lower ($p<0.01$) than during the initial observation period. The safety and efficacy of prophylactic treatment for periods longer than 3 months have not been established.

Factor VII deficiency
To January 2005, there were efficacy and safety data published on 60 patients with FVII deficiency treated with rFVIIa for 106 treatment episodes. The major part of the clinical experience is derived from 3 compassionate and 1 emergency use programs conducted by

Novo Nordisk between 1988 and 1999 on 30 patients with congenital FVII deficiency and 2 patients with acquired FVII deficiency (baseline level of FVII:C<5%) for a total of 69 treatment episodes. The primary endpoint of treatment was the effective haemostatic control of bleeds and prophylaxis in invasive and surgical procedures.

Summary of Efficacy and Safety of rFVIIa
The treatment with rFVIIa was rated as effective/excellent in 86% of serious bleeding episodes and in 96% of the surgical procedures. rFVIIa appeared to be equally effective in children and adults.

Two patients developed antibodies, in one of these cases the antibody was transient and both patients had received prior treatment with products containing plasma FVII.

Efficacy and Dose of rFVIIa
The clinical data shows a good efficacy-to-safety ratio when rFVIIa is used in a bolus injection treatment regimen of 15-30μg/kg at dosing intervals of 4-6 hours until haemostasis is secured. Smaller and greater doses of rFVIIa were used with effective outcome.

Glanzmann's Thrombasthenia
To November 2004, there were efficacy and safety data published on 89 patients with Glanzmann's Thrombasthenia treated with rFVIIa for 151 bleeds and 57 surgical procedures. The major part of the clinical experience is derived from the International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders which reported data on the use of rFVIIa in Glanzmann's Thrombasthenia between November 1995 and June 2001. The age of the patients ranged from 0.8 to 72 years. Disease severity based on the percentage of platelet GPIIb/IIIa complexes was known in 55 patients: 80% type I (GPIIb/IIIa <5% of normal), 13% type II (5-15%), and 7% variant-type (dysfunctional GPIIb/IIIa). A number of patients had a history of anti-GPIIb/IIIa or anti-HLA antibodies, or a history of refractoriness to platelet transfusion.

Amongst the 151 bleeding episodes treated with rFVIIa, nosebleeds were the most common (47%), followed by oropharyngeal (22.5%), miscellaneous (18.5%) and gastrointestinal bleeds (12%). rFVIIa was used in 57 invasive/surgical procedures: 10 major procedures, 26 minor procedures, and 21 dental extractions. The primary endpoint of treatment was the effective haemostatic control of bleeds and prophylaxis in invasive and surgical procedures. Treatment efficacy was considered for bleeds where no platelets were transfused during rFVIIa therapy (evaluable bleeds) with therapy considered effective where bleeding ceased within 48 hours of commencement of treatment with rFVIIa.

Summary of Efficacy and Safety of rFVIIa
Overall, the efficacy of rFVIIa in 147 evaluable bleeds ranged from 55%-79% with haemostasis secured in 61% of cases within 6 hours of the first injection. As prophylaxis for a wide variety of invasive and surgical procedures, rFVIIa was shown to provide effective coverage in 95.5% of the 45 evaluable procedures. The safety results support the safety profile observed to date with rFVIIa in the treatment of bleeding in haemophilia with inhibitors, with three serious adverse events possibly related to rFVIIa treatment reported. Of these three events, two were associated with continuous infusion.

Efficacy of NOVOSEVEN and the Presence of Anti-Platelet Antibodies or Platelet Refractoriness
Of the 57 evaluable bleeds in patients with platelet antibodies or platelet refractoriness recorded in the International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders, 74% were successfully treated and 7% recurred and treatment failed in 19%. Among the remaining 40 evaluable bleeding episodes in patients without platelet refractoriness and antibodies, 70% were successfully treated, 7% recurred and treatment

failed in 23%. Thus, no significant difference in efficacy was observed between patients with and without anti-platelet antibodies or platelet refractoriness.

Efficacy and Dose of rFVIIa
The clinical data shows a good efficacy-to-safety ratio when rFVIIa is used in a treatment regimen of bolus injection of 80-120µg/kg per injection at dosing intervals ≤ 2.5 hours with a minimum of 3 doses to secure effective haemostasis. The prophylaxis of invasive/surgical procedures may require a more prolonged use of rFVIIa depending on the extent of the procedures.

Name and Address

Novo Nordisk Pharmaceuticals Ltd
PO Box 51-268
Pakuranga
Auckland

Telephone: (09) 916 5590
Fax: (09) 916 5595

Date of Preparation

4 March 2014