

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). NOVOSEVEN's recombinant coagulation Factor VIIa (rFVIIa) 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 1.0mg/mL (50,000 IU/mL), sodium chloride 2.3mg/mL, calcium chloride dihydrate 1.5mg/mL, glycylglycine 1.3mg/mL, polysorbate 80 0.1mg/mL and mannitol 25mg/mL, sucrose 10mg/mL, methionine 0.5mg/mL and histidine 1.6mg/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

Pharmacotherapeutic group: Coagulation factors, ATC code: B02B D08.

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 to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of NOVOSEVEN RT activate factor X directly on the surface of activated platelets, localized to the site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independently of tissue factor. Accordingly, the pharmacodynamic effect of factor VIIa gives rise to an increased local formation of factor Xa, thrombin and fibrin.

A theoretical risk for the development of systemic activation of the coagulation system in patients suffering from under-lying diseases predisposing for 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 160µg rFVIIa per kg bodyweight and/or placebo (3 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) 35-70µg/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 FVIIa activity assay, the pharmacokinetic properties of rFVIIa were studied in 12 paediatric (2-12 years) and 5 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/kg x hr), 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 (70.8-79.1 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

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
<i>Inhibitors to coagulation Factors VIII or IX</i>	Control of Bleeding: 35-120µg/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: <ol style="list-style-type: none"> 1) Two to three injections of 90µg/kg body weight administered at three-hour intervals. 2) One single injection of 270µg/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 (270µg/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 administered as a once daily dose of 90µg/kg body weight for up to three months to reduce the frequency of bleeding.
	Surgical Prophylaxis: 35-120µg/kg every 2-3 hours for 1-2 days, then every 2-6 hours if continued treatment is necessary.
<i>Factor VII deficiency</i>	15-30µg/ per kg body weight every 4-6 hours until haemostasis is achieved. Dose and frequency of injections should be individually titrated.
<i>Glanzmann's thrombasthenia</i>	80-120µg/ per 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 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.

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.

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.

Contraindications

NOVOSEVEN RT should not be administered to patients with known hypersensitivity to any of the components of NOVOSEVEN RT. NOVOSEVEN RT is contraindicated in patients with known hypersensitivity to mouse, hamster or bovine protein.

Warnings and Precautions

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 thrombotic events or induction of Disseminated Intravascular Coagulation (DIC) in association with NOVOSEVEN RT 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 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.

As NOVOSEVEN RT contains trace amounts of mouse IgG protein (maximum of 1.2ng/mg rFVIIa), bovine IgG protein (maximum of 30ng/mg rFVIIa) and hamster and other bovine proteins (maximum of 19ng BHK protein/mg rFVIIa), there is a remote possibility that patients treated with NOVOSEVEN RT may develop hypersensitivity to these proteins.

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

If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately.

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 specialized in treatment of haemophilia patients with coagulation Factor VIII or IX inhibitors, or if not possible in close collaboration with a physician specialized 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. The risk of thrombosis in factor VII deficient patients treated with NOVOSEVEN RT is unknown.

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 3.0mg/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 270µg/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 5mg/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.

However, 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 NOVOSEVEN RT is excreted in human milk. Caution should be exercised when NOVOSEVEN is administered to nursing women.

Adverse Effects

Clinical trial data

rFVIIa has been generally well tolerated in clinical studies in 298 patients with haemophilia with inhibitors treated for 1,939 bleeding episodes. Table 2, below, lists adverse events that were reported in ≥1% of rFVIIa patients and were considered to be at least possibly related or of unknown relationship to rFVIIa administration.

Table 2

Body System Event	% of Haemophilia A or B Patients (n=298)
Body as a whole	
Fever	4
Headache	1
Pain	1
Platelets, Bleeding, and Clotting	
Haemorrhage NOS	3
Fibrinogen plasma decreased	2
DIC	1
Fibrinolysis increased	1
Skin and Musculoskeletal	
Haemarthrosis	3
Pruritus	1
Purpura	1
Rash	1
Cardiovascular	
Hypertension	2
Hypotension	1
Oedema	1

Events which were reported in less than 1% of patients and were considered to be at least possibly or of unknown relationship to rFVIIa administration were:

Whole Body: allergic reaction, anaphylactic shock

Skin and Musculo-skeletal: injection site reaction, arthrosis

Cardiovascular: bradycardia, tachycardia, angina pectoris, supraventricular tachycardia, circulatory shock, thrombophlebitis

Gastrointestinal: vomiting

Platelets, Bleeding, and Clotting: coagulation disorder, prothrombin decreased, decreased therapeutic response, thrombosis

Urinary system disorder: renal function abnormal, renal failure

Respiratory: pneumonia, pulmonary embolism

Central & Peripheral nervous system: ataxia, cerebrovascular disorder

Liver and biliary: Hepatic function abnormal

Two FVII deficient patients have developed antibodies against FVII after treatment with rFVIIa

Post-marketing data

The incidence of the adverse reactions listed below was derived from post-marketing experience with rFVIIa which included:

- 5 clinical trials in patients with inhibitors to coagulation Factors VIII and IX involving 298 patients for 1,939 treatment episodes, and
- adverse event reports from usage outside currently-approved indications

Based on post-marketing experience adverse drug reactions are rare (< 1 per 1,000 standard doses). When analysed by system organ classes, the reporting rates of adverse drug reactions during the post-marketing period, including both serious and non-serious reactions, are as indicated in Table 3 below:

Table 3: Adverse reactions reported in patients treated with rFVIIa

Blood and lymphatic disorders	
Very rare (<1/10,000)	Few cases of coagulopathic disorders, such as increased D-dimer and consumptive coagulopathy, have been reported. Patients at increased risk of disseminated intravascular coagulation, as described under 'Warnings and Precautions' should be carefully monitored.
Cardiac disorders	
Very rare (<1/10,000)	Myocardial infarction.
Gastrointestinal disorders	
Very rare (<1/10,000)	Few cases of nausea have been reported.
General disorders and administration site conditions	
Rare (> 1/10,000, <1/1,000)	Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of NOVOSEVEN RT is compliant with the recommended dosage as described under 'Dosage & Administration'. Fever may occur. Pain, especially at injection site may also occur on rare occasions.
Very rare (<1/10,000)	Injection site reaction
Investigations	
Very rare (<1/10,000)	Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin levels have been reported.
Nervous system disorders	
Very rare (<1/10,000)	Cerebrovascular disorders including cerebral infarction and cerebral ischaemia have been reported.
Rare (> 1/10,000, <1/1,000)	Headache
Skin and subcutaneous tissue disorders	
Very rare (<1/10,000)	Skin rashes (including allergic dermatitis and rash erythematous) may occur. Pruritus and urticaria.
Not known	Flushing, angioedema

Vascular disorders	
Rare (> 1/10,000, <1/1,000)	Arterial thrombotic events (such as myocardial infarction, cerebral infarction, ischaemia, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral arterial thrombosis, intestinal ischaemia and bowel infarction) have been reported.
Uncommon (> 1/1000, <1/100)	Venous thrombotic events (such as thrombophlebitis, superficial thrombophlebitis, thrombosis at i.v. site, renal vein thrombosis, intestinal ischaemia, deep vein thrombosis and related pulmonary embolism) have been reported. Patients at increased risk of venous thrombotic disorders due to concurrent conditions, previous history of thrombotic events, post surgery immobilisation or venous catheterisation should be carefully monitored. Thrombotic events of the liver including portal vein thrombosis. In the vast majority of cases the patients were predisposed due to liver disease or surgery. Incidents of haemorrhage have been reported. NOVOSEVEN is not expected to precipitate haemorrhage, but pre-existing haemorrhage may continue in case of insufficient efficacy or sub-optimal dosage regimen.
Rare (> 1/10,000, <1/1,000)	Angina pectoris
Not known	Intracardiac thrombus

Isolated cases of hypersensitivity reactions including anaphylactic reactions have been reported post marketing. Patients with a history of allergic reactions should be carefully monitored.

Arterial thromboembolic events in patients with acquired haemophilia have a frequency of 'common' (>1/100, <1/10).

When NOVOSEVEN RT is administered to patients outside current approved indications, arterial thromboembolic events are common ($\geq 1/100$ to $<1/10$). A higher risk of arterial thromboembolic adverse events (see Table 3 – 'Vascular disorders') (5.6% in patients treated with NOVOSEVEN RT versus 3.0% 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.

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 regions rich in fibrinolytic activity, such as the oral cavity.

Experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is however limited.

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 5U/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 > 5U/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 30µg/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 thrombotic event has been reported in an elderly (> 80 year) male patient with factor VII deficiency treated with 10 - 20 times the recommended dose.

A few cases of overdose have been reported in patients with haemophilia. In addition, the development of antibodies against NOVOSEVEN and FVII has been associated with overdose in one patient with factor VII deficiency.

Pharmaceutical Precautions

Store powder and solvent below 25°C and protected from light. 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 2°C to 8°C for not more than 24 hours.

Freezing should be avoided to prevent damage to the diluent vial.

Medicine Classification

General Sale Medicine.

Package Quantities

The NovoSeven pack contains a single use glass vial of 1.0mg (50,000IU), or 2.0mg (100,000IU), or 5.0mg (250,000IU), white, lyophilised powder (NovoSeven RT) and a solvent vial. The 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 L-histidine in water for injection and is supplied as a clear colourless solution, and referred to as the solvent vial. 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.

1.0 mg/vial Recombinant Coagulation Factor VIIa
1.1 ml solvent for reconstitution.

2.0 mg/vial Recombinant Coagulation Factor VIIa
2.1 ml solvent for reconstitution.

5.0 mg/vial Recombinant Coagulation Factor VIIa
5.2 ml solvent for reconstitution.

Each pack contains one vial of white powder for solution for injection and one vial of solvent for reconstitution.

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.

Qualitative Composition

Recombinant Coagulation Factor VIIa. Human Factor VII was cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant Factor VII is secreted from the BHK cells and is activated during the purification procedure. NOVOSEVEN Recombinant Coagulation Factor VIIa is structurally very similar to plasma-derived activated Factor VII (Human).

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)
Water for injections

Solvent

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

After reconstitution with the appropriate volume of diluent, each vial contains NOVOSEVEN RT 1.0 mg/ml (50 KIU/ml). After reconstitution, 1 ml of solution contains 10 mg sucrose and 2.3 mg sodium chloride.

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 4. 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 4: Clinical trials of rFVIIa

Control of bleeding in patients with inhibitors to coagulation Factors VIII and IX

Study	Bleeding indication	No. Pts (bleeds)	Dose $\mu\text{g}/\text{kg}$	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 muscle	6 (13) 10 (20)	35 70	q3-4h	6.5 (av) 4.7 (av)	55 47	- 50

Studies 04 and 05 were randomised dose comparisons of 35 and 70 $\mu\text{g}/\text{kg}$. 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 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ regimen with a standard regimen of 3 doses of 90 $\mu\text{g}/\text{kg}$ 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 5: 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.

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