1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 1 mg (50 KIU) powder and solvent for solution for injection
NovoSeven 2 mg (100 KIU) powder and solvent for solution for injection
NovoSeven 5 mg (250 KIU) powder and solvent for solution for injection
NovoSeven 8 mg (400 KIU) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven 1 mg (50 KIU)
NovoSeven is presented as powder and solvent for solution for injection containing 1 mg eptacog alfa (activated) per vial (corresponds to 50 KIU/vial).

NovoSeven 2 mg (100 KIU)
NovoSeven is presented as powder and solvent for solution for injection containing 2 mg eptacog alfa (activated) per vial (corresponds to 100 KIU/vial).

NovoSeven 5 mg (250 KIU)
NovoSeven is presented as powder and solvent for solution for injection containing 5 mg eptacog alfa (activated) per vial (corresponds to 250 KIU/vial).

NovoSeven 8 mg (400 KIU)
NovoSeven is presented as powder and solvent for solution for injection containing 8 mg eptacog alfa (activated) per vial (corresponds to 400 KIU/vial).

1 KIU equals 1,000 IU (International Units).

eptacog alfa (activated) is recombinant coagulation factor VIIa (rFVIIa) with a molecular mass of approximately 50,000 Daltons produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology.

After reconstitution, the product contains 1 mg/ml eptacog alfa (activated) when reconstituted with solvent.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White lyophilised powder. Solvent: clear colourless solution. The reconstituted solution has a pH of approximately 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NovoSeven is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
- in patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
- in patients with acquired haemophilia

[no notes on this page]

- in patients with congenital FVII deficiency
- in patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available.

Severe postpartum haemorrhage
NovoSeven is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders.

In the management of severe postpartum haemorrhage, appropriate multidisciplinary expertise should be consulted. In addition to obstetricians, this includes anaesthesiologists, critical care specialists and/or haematologists. Standard management practices should remain implemented, based on the individual patient's requirements. Maintenance of adequate fibrinogen concentration and platelet count is recommended in order to optimise the benefit of NovoSeven treatment.

Posology

Haemophilia A or B with inhibitors or expected to have a high anamnestic response

Dose
NovoSeven should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight. Following the initial dose of NovoSeven further injections may be repeated. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage, the invasive procedures or surgery being performed.

Paediatric population
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 (see section 5.2).

Dose interval
Initially 2 – 3 hours to obtain haemostasis.
If continued therapy is needed, the dose interval can be increased successively once effective haemostasis is achieved to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated.

Mild to moderate bleeding episodes (including home therapy)
Early intervention has been shown to be efficacious in the treatment of mild to moderate joint, muscle and mucocutaneous bleeds. Two dosing regimens can be recommended:

1) Two to three injections of 90 µg per kg body weight administered at three-hour intervals. If further treatment is required, one additional dose of 90 µg per kg body weight can be administered.
2) One single injection of 270 µg per kg body weight.

The duration of home therapy should not exceed 24 hours. Only after consultation with the haemophilia treatment centre can continued home treatment be considered.

There is no clinical experience with administration of a single dose of 270 µg per kg body weight in elderly patients.

[no notes on this page]

Serious bleeding episodes
An initial dose of 90 µg per kg body weight is recommended and could be administered on the way to the hospital where the patient is usually treated. The following dose varies according to the type and severity of the haemorrhage. Dosing frequency should initially be every second hour until clinical improvement is observed. If continued therapy is indicated, the dose interval can then be increased to 3 hours for 1 – 2 days. Thereafter, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated. A major bleeding episode may be treated for 2 – 3 weeks but can be extended beyond this if clinically warranted.

Invasive procedure/surgery
An initial dose of 90 µg per kg body weight should be given immediately before the intervention. The dose should be repeated after 2 hours and then at 2 – 3 hour intervals for the first 24 – 48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2 – 4 hour intervals for 6 – 7 days. The dose interval may then be increased to 6 – 8 hours for another 2 weeks of treatment.
Patients undergoing major surgery may be treated for up to 2 – 3 weeks until healing has occurred.

Acquired Haemophilia

Dose and dose interval
NovoSeven should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight. Following the initial dose of NovoSeven further injections may be given if required. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage, the invasive procedures or the surgery being performed.
The initial dose interval should be 2 – 3 hours. Once haemostasis has been achieved, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged to be indicated.

Factor VII deficiency

Dose, dose range and dose interval
The recommended dose range in adults and children for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 15 – 30 µg per kg body weight every 4 – 6 hours until haemostasis is achieved. Dose and frequency of injections should be adapted to each individual.

Paediatric population
Limited clinical experience in long term prophylaxis has been gathered in the paediatric population below 12 years of age, with a severe clinical phenotype (see section 5.1).

Dose and frequency of injections for prophylaxis should be based on clinical response and adapted to each individual.

Glanzmann's thrombasthenia

Dose, dose range and dose interval
The recommended dose for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 90 µg (range 80 – 120 µg) per kg body weight at intervals of two hours (1.5 – 2.5 hours). At least three doses should be administered to secure effective haemostasis. The recommended route of administration is bolus injection as lack of efficacy may appear in connection with continuous infusion.

For those patients who are not refractory, platelets is the first line treatment for Glanzmann's thrombasthenia.

[no notes on this page]

Severe postpartum haemorrhage

Dose range and dose interval
The recommended dose range for the treatment of bleeding is 60 – 90 µg per kg body weight administered by intravenous bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on clinical response of the individual patient.
It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.

Method of administration
For instructions on reconstitution of the medicinal product before administration, see section 6.6.
Administer the solution as an intravenous bolus injection over 2 – 5 minutes.

Monitoring of treatment – laboratory tests

There is no requirement for monitoring of NovoSeven therapy. Severity of bleeding condition and clinical response to NovoSeven administration must guide dosing requirements.

After administration of rFVIIa, prothrombin time (PT) and activated partial thromboplastin time (aPTT) have been shown to shorten, however no correlation has been demonstrated between PT and aPTT and clinical efficacy of rFVIIa.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to mouse, hamster or bovine protein.

4.4 Special warnings and precautions for use

In pathological conditions in which tissue factor may be expressed more extensively than considered normal, there may be a risk of development of thrombotic events or induction of Disseminated Intravascular Coagulation (DIC) in association with NovoSeven 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 to patients with a history of coronary heart disease, to patients with liver disease, to post-operative patients, to pregnant or peripartum women, to neonates, or to patients at risk of thromboembolic events or DIC. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

In severe postpartum haemorrhage and pregnancy, the clinical conditions (delivery, severe haemorrhage, transfusion, DIC, surgery/invasive procedures and coagulopathy) are known contributing factors to the thromboembolic risk; and in particular venous thromboembolic risk associated with the administration of NovoSeven (see section 4.8).

As recombinant coagulation factor VIIa NovoSeven may contain trace amounts of mouse IgG, bovine IgG and other residual culture proteins (hamster and bovine serum proteins), the remote possibility exists that patients treated with the product may develop hypersensitivity to these proteins. In such cases treatment with antihistamines i.v. should be considered.

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

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

[no notes on this page]

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 usages of NovoSeven.

Factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity before and after administration of NovoSeven. 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 NovoSeven during surgery but the risk of thrombosis in factor VII deficient patients treated with NovoSeven is unknown (see section 5.1).

Sodium content
The medicinal product contains less than 1 mmol sodium (23 mg) per injection, indicating that it is essentially 'sodium free'.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

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

Antifibrinolytics 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. Antifibrinolytics are also used to reduce blood loss in women with postpartum haemorrhage. Experience with concomitant administration of antifibrinolytics and rFVIIa treatment is, however, limited.

Based on a non-clinical study (see section 5.3) it is not recommended to combine rFVIIa and rFXIII. There are no clinical data available on interaction between rFVIIa and rFXIII.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a precautionary measure, it is preferable to avoid use of NovoSeven 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. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Breast-feeding

It is unknown whether rFVIIa is excreted in human breast milk. 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 NovoSeven should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven therapy to the woman.

Fertility

Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility.

[no notes on this page]

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions are decreased therapeutic response, pyrexia, rash, venous thromboembolic events, pruritus and urticaria. These reactions are reported as uncommon (≥ 1/1,000, < 1/100).

Tabulated summary of adverse reactions

Table 1 lists adverse reactions reported during clinical trials and from spontaneous (post-marketing) reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reactions reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of 'not known'.

Clinical trials conducted in 484 patients (including 4297 treatment episodes) with haemophilia A and B, acquired haemophilia, factor VII deficiency or Glanzmann's thrombasthenia have shown that adverse drug reactions are common (≥ 1/100 to < 1/10). As the total number of treatment episodes in clinical trials is below 10,000, the lowest possible frequency of adverse drug reactions that can be assigned is rare (≥ 1/10,000 to < 1/1,000).

The most frequent adverse drug reactions are pyrexia and rash (uncommon: ≥ 1/1,000 to < 1/100), and the most serious adverse drug reactions include venous thromboembolic events (uncommon: ≥ 1/1,000 to < 1/100) and arterial thromboembolic events (rare: ≥ 1/10,000 to < 1/1,000).

The frequencies of both serious and non-serious adverse drug reactions are listed by system organ classes in the table below

Table 1 Adverse reactions from clinical trials and spontaneous (post-marketing) reports

MedDRA system organ class	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency Not Known
Blood and lymphatic system disorders		- Disseminated intravascular coagulation (see section 4.4) - Related laboratory findings, including elevated levels of D-dimer and decreased levels of AT (see section 4.4) - Coagulopathy	
Gastrointestinal disorders		- Nausea	

[no notes on this page]

General disorders and administration site conditions	- Therapeutic response decreased* - Pyrexia	- Injection site reaction including injection site pain	
Immune system disorders		- Hypersensitivity (see sections 4.3 and 4.4)	- Anaphylactic reaction
Investigations		- Increased fibrin degradation products - Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin	
Nervous system disorders		- Headache	
Skin and subcutaneous tissue disorders	- Rash (including allergic dermatitis and rash erythematous) - Pruritus and urticaria		- Flushing - Angioedema
Vascular disorders	- 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)	- 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) - Angina pectoris	- Intracardiac thrombus

* Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of NovoSeven is compliant with the recommended dosage as stated in section 4.2.

Description of selected adverse reactions

Inhibitory antibody formation

In post-marketing experience, there have been no reports of inhibitory antibodies against NovoSeven 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.

[no notes on this page]

In clinical trials of patients with factor VII deficiency, formation of antibodies against NovoSeven 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, were present. Patients with factor VII deficiency treated with NovoSeven should be monitored for factor VII antibodies (see section 4.4).

Thromboembolic events - arterial and venous

When NovoSeven 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: Vascular disorders) (5.6% in patients treated with NovoSeven 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.

Safety and efficacy of NovoSeven have not been established outside the approved indications and therefore NovoSeven should not be used.

Thromboembolic events may lead to cardiac arrest.

Other special populations

Patients with acquired haemophilia

Clinical trials conducted in 61 patients with acquired haemophilia with a total of 100 treatment episodes, showed that certain adverse drug reactions were reported more frequently (1% based on treatment episodes): Arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products.

Women with severe postpartum haemorrhage

In an open-label randomised clinical trial, venous thromboembolic events were reported in 2 of 51 patients treated with a single dose of NovoSeven (median dose 58 µg/kg) and none of 33 patients not treated with NovoSeven; no arterial thromboembolic events were reported in either group.
In 4 non-interventional studies, venous thromboembolic events were reported in 3 of 358 (0.8%) patients treated with NovoSeven (median dose range 63-105 µg/kg) and arterial thromboembolic events were reported in 1 (0.3%) patient treated with NovoSeven.

For known contributing factors to thromboembolic risk associated with pregnancy and severe postpartum haemorrhage, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

Belgium
Federal Agency for Medicines and Health Products
Vigilance Division
PO Box 97
B-1000 Brussels Madou
Website: www.famhp.be/en/side_effect
e-mail: adr@fagg-afmps.be

[no notes on this page]

Luxembourg
Centre Régional de Pharmacovigilance de Nancy
Bâtiment de Biologie Moléculaire et de Biopathologie (BBB)
CHRU de Nancy – Hôpitaux de Brabois
Rue du Morvan
54511 VANDOEUVRE LES NANCY CEDEX
Tel.: (+33) 3 83 65 60 85 / 87
e-mail: crpv@chru-nancy.fr
or
Direction de la Santé
Division de la Pharmacie et des Médicaments
20, rue de Bitbourg
L-1273 Luxembourg-Hamm
Tel.: (+352) 2478 5592
e-mail: pharmacovigilance@ms.etat.lu
Link to the form: https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html

4.9 Overdose

Dose limiting toxicities of NovoSeven have not been investigated in clinical trials.

Four cases of overdose have been reported in patients with haemophilia in 16 years. 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 year) 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood coagulation factors, ATC code: B02BD08

Mechanism of action
NovoSeven contains activated recombinant coagulation factor VII. The mechanism of action includes the binding of factor VIIa to exposed tissue factor. This complex activates factor IX into factor IXa and factor X into factor Xa, leading to the initial conversion of small amounts 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 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.

Pharmacodynamic effects
The pharmacodynamic effect of factor VIIa gives rise to an increased local formation of factor Xa,

[no notes on this page]

thrombin and fibrin.

The time to peak coagulant activity after administration of NovoSeven was approximately 10 minutes in healthy subjects and patients with haemophilia.

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

Clinical efficacy and safety

Congenital FVII deficiency

In an observational registry (F7HAEM-3578) covering subjects with congenital FVII deficiency, the median dose for long term prophylaxis against bleeding in 22 paediatric patients (below 12 years of age) with Factor VII deficiency and a severe clinical phenotype was 30 µg/kg (range 17 µg/kg to 200 µg/kg; the dose most often used was 30 µg/kg in 10 patients) with a median dose frequency of 3 doses per week (range 1 to 7; the dose frequency most often reported was 3 per week in 13 patients).

In the same registry 3 out of 91 surgical patients experienced thromboembolic events.

Glanzmann's thrombasthenia

An observational registry (F7HAEM-3521) covered 133 subjects with Glanzmann's thrombasthenia treated with NovoSeven. The median dose per infusion for treatment of 333 bleeding episodes was 90 µg/kg (range 28 to 450 µg/kg). NovoSeven was used in 157 surgical procedures, at a median dose of 92 µg/kg (up to 270 µg/kg). Treatment with NovoSeven, alone or in combination with antifibrinolytics and/or platelets, was defined as effective when bleeding was stopped for at least 6 hours. The efficacy rates were 81% and 82%, respectively, in patients with positive or negative refractoriness to platelet transfusions, and 77% and 85%, respectively, in patients testing positive or negative for antibodies to platelets. Positive status indicates at least one positive test at any admission.

Severe postpartum haemorrhage

The efficacy and safety of NovoSeven was assessed in 84 women with severe postpartum haemorrhage in a multicentre, open-label clinical trial. Patients were randomised either to treatment with a single dose of 60 µg/kg of NovoSeven (in addition to standard of care; N=42) or to reference therapy (standard of care alone; N=42), following failure of uterotonics (sulprostone). The treatment groups were well balanced in terms of demographic characteristics and postpartum haemorrhage treatment prior to randomisation. Fibrinogen and tranexamic acid were part of standard of care. Information on fibrinogen/tranexamic acid use was available from approximately 57% of patients in the NovoSeven group and 43% of patients in the reference group. Of these, about 40% of the patients in both groups received fibrinogen and/or tranexamic acid. Bleeding was considered to have stopped (i.e. treatment success) if the estimated blood flow decreased to less than 50 ml per 10 minutes within the 30 minutes following randomisation. If the bleeding was uncontrolled or intractable, invasive procedures were considered.

In the primary analysis, fewer women in the NovoSeven group (21 vs 35) had at least one embolisation and/or ligation procedure compared to the reference group, corresponding to a statistically significant 40% relative reduction in risk for the NovoSeven group compared to the reference group (relative risk = 0.60 (95% confidence interval: 0.43 – 0.84, p=0.0012)).

In the reference group, 8 of the 42 patients received late NovoSeven as a compassionate treatment in an attempt to avoid salvage hysterectomy, which succeeded in 2 cases.

5.2 Pharmacokinetic properties

Healthy subjects

[no notes on this page]

Distribution, elimination and linearity
Using the FVII clotting assay, the pharmacokinetics of rFVIIa were investigated in 35 healthy Caucasian and Japanese subjects in a dose-escalation study. Subjects were stratified according to sex and ethnic group and dosed with 40, 80 and 160 µg rFVIIa per kg body weight (3 doses each) and/or placebo. The pharmacokinetics were similar across sex and ethnic groups.
The mean steady state volume of distribution ranged from 130 to 165 ml/kg, the mean values of clearance ranged from 33.3 to 37.2 ml/h×kg.
The mean terminal half-life ranged from 3.9 to 6.0 hours.
The pharmacokinetic profiles indicated dose proportionality.

Haemophilia A and B with inhibitors

Distribution, elimination and linearity
Using the FVIIa assay, the pharmacokinetic properties of rFVIIa were studied in 12 paediatric (2 – 12 years) and 5 adult patients in non-bleeding state.
Mean volume of distribution at steady state was 196 ml/kg in paediatric patients versus 159 ml/kg in adults.
Mean clearance was approximately 50% higher in paediatric patients relative to adults (78 versus 53 ml/h×kg), whereas the mean terminal half-life was determined to 2.3 hours in both groups.
Clearance appears related with age, therefore in younger patients clearance may be increased by more than 50%.
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).

Factor VII deficiency

Distribution and elimination
Single dose pharmacokinetics of rFVIIa, 15 and 30 µg per kg body weight, showed no significant difference between the two doses used with regard to dose-independent parameters:
Volume of distribution at steady state (280 – 290 ml/kg), half-life (2.82 – 3.11 h), total body clearance (70.8 – 79.1 ml/h×kg) and mean residence time (3.75 – 3.80 h).
The mean *in vivo* plasma recovery was approximately 20%.

Glanzmann's thrombasthenia

Pharmacokinetics of NovoSeven in patients with Glanzmann's thrombasthenia have not been investigated, but are expected to be similar to the pharmacokinetics in haemophilia A and B patients.

Severe postpartum haemorrhage

Pharmacokinetics of NovoSeven in patients with severe postpartum haemorrhage have not been investigated.

5.3 Preclinical safety data

All findings in the preclinical safety programme were related to the pharmacological effect of rFVIIa.

A potential synergistic effect of combined treatment with rFXIII and rFVIIa in an advanced cardiovascular model in cynomolgus monkey resulted in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[no notes on this page]

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

6.2 Incompatibilities

NovoSeven must not be mixed with infusion solutions or be given in a drip.

6.3 Shelf life

The shelf life for the product packed for sale is 3 years when the product is stored below 25°C.

In vial
After reconstitution, chemical and physical stability has been demonstrated for 6 hours at 25°C and 24 hours at 5°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, storage time and storage conditions prior to use are the responsibility of the user, and should not be longer than 24 hours at 2°C – 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. The reconstituted solution should be stored in the vial.

In syringe (50 ml polypropylene) in hospital settings only
Reconstitution must take place in controlled and validated aseptic conditions by adequately trained staff. Under these conditions, chemical and physical stability has been demonstrated for 24 hours at 25°C when stored in a 50 ml syringe (polypropylene). If not used immediately, the conditions prior to use are the responsibility of the user and the in-use storage time must not be longer than as stated above.

6.4 Special precautions for storage

– Store powder and solvent below 25°C.
– Store powder and solvent protected from light.
– Do not freeze.
– For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

The solvent of NovoSeven is provided in a pre-filled syringe. Not all presentations may be marketed.

The NovoSeven 1 mg (50 KIU)/NovoSeven 2 mg (100 KIU) package contains

– 1 vial (2 ml) with white powder for solution for injection
– 1 pre-filled syringe (3 ml) with solvent for reconstitution
– 1 plunger rod
– 1 vial adapter, with an integrated particle filter with a pore size of 25 micrometer.

[no notes on this page]

The NovoSeven 5 mg (250 KIU)/NovoSeven 8 mg (400 KIU) package contains

– 1 vial (12 ml) with white powder for solution for injection
– 1 pre-filled syringe (10 ml) with solvent for reconstitution
– 1 plunger rod
– 1 vial adapter, with an integrated particle filter with a pore size of 25 micrometer.

Vial: Type I glass vial closed with a chlorobutyl rubber stopper, covered with an aluminium cap. The closed vial is equipped with a polypropylene tamper-evident snap-off cap.

Pre-filled syringe: Type I glass barrel with a polypropylene backstop and bromobutyl rubber plunger. The syringe cap consists of bromobutyl rubber and polypropylene tamper evident seal.

Plunger rod: made of polypropylene.

6.6 Special precautions for disposal and other handling

The solvent of NovoSeven is provided in a pre-filled syringe. Not all presentations may be marketed. Handling procedures are described below.

Powder in vial and solvent in pre-filled syringe:

Always use an aseptic technique.

Reconstitution

- The NovoSeven powder vial and pre-filled syringe with solvent should be at room temperature at reconstitution. Remove the plastic cap from the vial. If the cap is loose or missing, do not use the vial. Wipe the rubber stopper on the vial with a sterile alcohol swab and allow it to dry for a few seconds before use. Do not touch the rubber stopper after wiping it.

- Remove the protective paper from the vial adapter. Do not take the vial adapter out of the protective cap. If the protective paper is not fully sealed or it is broken do not use the vial adapter. Turn over the protective cap, and snap the vial adapter onto the vial. Lightly squeeze the protective cap with the thumb and index finger. Remove the protective cap from the vial adapter.

- Screw the plunger rod clockwise into the plunger inside the pre-filled syringe until resistance is felt. Remove the syringe cap from the pre-filled syringe by bending it down until the perforation breaks. Do not touch the syringe tip under the syringe cap. If the syringe cap is loose or missing, do not use the pre-filled syringe.

- Screw the pre-filled syringe securely onto the vial adapter until resistance is felt. Hold the pre-filled syringe slightly tilted with the vial pointing downwards. Push the plunger rod to inject all the solvent into the vial. Keep the plunger rod pressed down and swirl the vial gently until all the powder is dissolved. Do not shake the vial as this will cause foaming.

If a larger dose is needed, repeat the procedure with additional vials, pre-filled syringes and vial adapters.

The NovoSeven reconstituted solution is colourless and should be inspected visually for particulate matter and discolouration prior to administration.

It is recommended to use NovoSeven immediately after reconstitution. For storage conditions of the reconstituted medicinal product, see section 6.3.

[no notes on this page]

Administration

- Keep the plunger rod pushed completely in. Turn the syringe with the vial upside down. Stop pushing the plunger rod and let it move back on its own while the reconstituted solution fills the syringe. Pull the plunger rod slightly downwards to draw the mixed solution into the syringe.

- While holding the vial upside down, tap the syringe gently to let any air bubbles rise to the top. Push the plunger rod slowly until all air bubbles are gone.

  If the entire dose is not required, use the scale on the syringe to see how much mixed solution is withdrawn.

- Unscrew the vial adapter with the vial.

- NovoSeven is now ready for injection. Locate a suitable site, and slowly inject NovoSeven into a vein over a period of 2 – 5 minutes without removing the needle from the injection site.

Safely dispose of the used materials. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Procedure for pooling of vials for hospital use only:

During in vitro studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 25°C in a 50 ml syringe (polypropylene). Compatibility with the product was demonstrated for the system consisting of a 50 ml syringe (polypropylene), a 2 m infusion tube (polyethylene) and an in-line filter with a 5 micrometer pore size.

Pooling of vials (hospital use only):

- All steps should be completed under controlled and validated aseptic conditions by adequately trained staff.
- If not reconstituted, pooled or used as recommended the in-use times and conditions prior to use are the responsibility of the user.
- Ensure that a vial adapter is used.
- Reconstitute the product as described above under *Reconstitution.* Unscrew the empty syringe from the vial adapter and ensure that a vial adapter is attached to the vial containing reconstituted product.
- Repeat the procedure with the appropriate number of additional vials, pre-filled syringes and vial adapters.
- Draw approximately 5 ml of sterile air into the 50 ml syringe (polypropylene). Screw the syringe securely onto the vial adapter until resistance is felt. Hold the syringe slightly tilted with the vial pointing downwards. Push the plunger rod gently to inject a little air into the vial. Turn the syringe with the vial upside down and withdraw the contents of the vial into the syringe.
- Repeat the above procedure with the remaining vials with reconstituted product, to obtain the desired volume in the syringe.
- An in-line filter with a 5 micrometer pore size must be ensured for administration. Ensure that the syringe, the infusion tube and the in-line filter are primed and free of air before administration.
- The syringe with adequately reconstituted product is now ready for administration in a CE-marked infusion pump (accepting a 50 ml syringe).
- The infusion pump must only be operated by trained hospital personnel.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

[no notes on this page]

Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

NovoSeven 1 mg (50 KIU)

EU/1/96/006/008

NovoSeven 2 mg (100 KIU)

EU/1/96/006/009

NovoSeven 5 mg (250 KIU)

EU/1/96/006/010

NovoSeven 8 mg (400 KIU)

EU/1/96/006/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 1996
Date of latest renewal: 09 February 2006

10. DATE OF REVISION OF THE TEXT

05/2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.

[no notes on this page]