ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

- 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.

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.

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 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.

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	
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.

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 listed in Appendix V.

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, 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

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

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.

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.

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.

<u>Procedure for pooling of vials for hospital use only:</u>

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 in-line filters within the range of 0.2 to 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 within the range of 0.2 to 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
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

01/2023

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines webportal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 1 mg
Powder and solvent for solution for injection
eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

eptacog alfa (activated) 1 mg/vial (50 KIU/vial), 1 mg/ml after reconstitution

3. LIST OF EXCIPIENTS

Sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, histidine, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:
1 vial of powder
1 pre-filled syringe of solvent with separate plunger rod
1 vial adapter for reconstitution

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use. For single dose administration
Administration should preferably take place immediately after reconstitution
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP/

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Do not freeze
Store protected from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/96/006/008

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoSeven 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven 1 mg
Powder for injection
eptacog alfa (activated)
IV

2. METHOD OF ADMINISTRATION

For single dose injection

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for pre-filled syringe with solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for NovoSeven

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

1
2
3
ml

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 2 mg
Powder and solvent for solution for injection
eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

eptacog alfa (activated) 2 mg/vial (100 KIU/vial), 1 mg/ml after reconstitution

3. LIST OF EXCIPIENTS

Sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, histidine, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:
1 vial of powder
1 pre-filled syringe of solvent with separate plunger rod
1 vial adapter for reconstitution

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use. For single dose administration
Administration should preferably take place immediately after reconstitution
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP/

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Do not freeze
Store protected from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/96/006/009

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoSeven 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven 2 mg
Powder for injection
eptacog alfa (activated)
IV

2. METHOD OF ADMINISTRATION

For single dose injection

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for pre-filled syringe with solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for NovoSeven

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

1
2
3
ml

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 5 mg
Powder and solvent for solution for injection
eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

eptacog alfa (activated) 5 mg/vial (250 KIU/vial), 1 mg/ml after reconstitution

3. LIST OF EXCIPIENTS

Sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, histidine, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:
1 vial of powder
1 pre-filled syringe of solvent with separate plunger rod
1 vial adapter for reconstitution

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use. For single dose administration
Administration should preferably take place immediately after reconstitution
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP/

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Do not freeze
Store protected from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/96/006/010

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoSeven 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven 5 mg
Powder for injection
eptacog alfa (activated)
IV

2. METHOD OF ADMINISTRATION

For single dose injection

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for pre-filled syringe with solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for NovoSeven

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

1
2
3
4
5
6
7
8
9
10
ml

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 8 mg
Powder and solvent for solution for injection
eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

eptacog alfa (activated) 8 mg/vial (400 KIU/vial), 1 mg/ml after reconstitution

3. LIST OF EXCIPIENTS

Sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, histidine, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:
1 vial of powder
1 pre-filled syringe of solvent with separate plunger rod
1 vial adapter for reconstitution

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use. For single dose administration
Administration should preferably take place immediately after reconstitution
Read package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP/

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Do not freeze
Store protected from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

12. MARKETING AUTHORISATION NUMBER

EU/1/96/006/011

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NovoSeven 8 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven 8 mg
Powder for injection
eptacog alfa (activated)
IV

2. METHOD OF ADMINISTRATION

For single dose injection

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 mg

6. OTHER

Novo Nordisk A/S

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for pre-filled syringe with solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for NovoSeven

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8 ml

6. OTHER

1
2
3
4
5
6
7
8
9
10
ml

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

eptacog alfa (activated)

Read all of this leaflet carefully before you are given this injection because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NovoSeven is and what it is used for

NovoSeven is a blood coagulation factor. It works by making the blood clot at the site of bleeding, when the body's own clotting factors are not working.

NovoSeven is used to treat bleeding, and to prevent excessive bleeding after surgery or other important treatments. Early treatment with NovoSeven reduces how much you bleed and for how long. It works in all types of bleeds, including joint bleeds. This reduces the need for hospitalisation and days absent from work and school.
It is used in certain groups of people:
- If you were *born with haemophilia* and do not respond normally to factors VIII or IX treatment
- If you have *acquired haemophilia*
- If you have *Factor VII deficiency*
- If you have *Glanzmann's thrombasthenia* (a bleeding disorder) and your condition cannot be treated effectively with platelet transfusion, or if platelets are not readily available.

NovoSeven can also be given to you by a doctor to treat heavy bleeding after delivery of your baby, even if you do not have a bleeding disorder.

2. What you need to know before you use NovoSeven

Do not use NovoSeven
- If you are allergic to eptacog alfa (active compound of NovoSeven) or any of the other ingredients in this medicine (listed in section 6).
- If you are allergic to mouse, hamster or cow proteins (such as cows' milk).

► If any of these apply to you, do not use NovoSeven. Talk to your doctor.

Warnings and precautions
Before treatment with NovoSeven, make sure your doctor knows:
- If you have just had surgery
- If you recently had a crush injury
- If your arteries are narrowed by disease (atherosclerosis)
- If you have an increased risk of blood clots (thrombosis)
- If you have severe liver disease
- If you have a serious blood infection
- If you are prone to *disseminated intravascular coagulation* (DIC, a condition where blood clots develop throughout the blood stream) you must be carefully monitored.

► If any of these conditions apply to you, talk to your doctor before using the injection.

Other medicines and NovoSeven
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not use NovoSeven at the same time as *prothrombin complex concentrates* or rFXIII. You should talk to your doctor before using NovoSeven if you also use Factor VIII or IX products.

There is limited experience of using NovoSeven together with medicines called *antifibrinolytic drugs* (such as aminocaproic acid or tranexamic acid) which are also used to control bleeding. You should talk to your doctor before using NovoSeven with these medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you use NovoSeven.

Driving and using machines
There are no studies on the effect of NovoSeven on the ability to drive and use machines. However, there is no medical reason to think that it would affect your ability.

NovoSeven contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per injection, i.e. essentially 'sodium-free'.

3. How to use NovoSeven

The NovoSeven powder must be reconstituted with its solvent and injected into a vein. See overleaf for detailed instructions.

When to treat yourself
Start treatment of a bleed as early as possible, ideally within 2 hours.
- In cases of a mild or moderate bleed, you should treat yourself as early as possible, ideally at home.
- In case of a severe bleed you should contact your doctor. Usually severe bleeds are treated at the hospital and you can give yourself the first NovoSeven dose on the way there.

Do not treat yourself for longer than 24 hours without consulting your doctor.
- Each time you use NovoSeven, tell your doctor or hospital as soon as possible.
- If bleeding is not controlled within 24 hours, contact your doctor immediately. You will usually need hospital care.

Dose
The first dose should be given as early as possible after bleeding has started. Talk to your doctor about when to use the injections and how long to keep using them.
The dose will be worked out by your doctor, based on your body weight, condition and type of bleed. To achieve the best results, follow the prescribed dose carefully. Your doctor might change the dose.

If you have haemophilia:
The usual dose is 90 micrograms for every 1 kilogram you weigh; you can repeat the injection every 2–3 hours until bleeding is controlled.
Your doctor may recommend a single dose of 270 micrograms for every 1 kilogram you weigh. There is no clinical experience in people over 65 using this single dose.

If you have Factor VII deficiency:
The usual dose range is 15 to 30 micrograms for every 1 kilogram you weigh, for each injection.

If you have Glanzmann's thrombasthenia:
The usual dose is 90 micrograms (range is 80 to 120 micrograms) for every 1 kilogram you weigh, for each injection.

If you inject more NovoSeven than you should
If you inject too much NovoSeven, get medical advice at once.

If you forget an injection of NovoSeven
If you forget an injection, or if you want to stop the treatment, get your doctor's advice.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Rare *(may affect up to 1 in 1,000 treatment episodes)*
- Allergic, hypersensitivity or anaphylactic reactions. Signs may include skin rashes, itching, flushing and hives; wheezing or difficulty breathing; feeling faint or dizzy; and severe swelling of the lips or throat, or at the injection site.
- Blood clots in arteries in the heart (which could lead to a heart attack or angina), in the brain (which could lead to a stroke) or in the intestine and kidneys. Signs may include severe pain in the chest, breathlessness, confusion, difficulty with speech or movement (paralysis) or abdominal pain.

Uncommon *(may affect up to 1 in 100 treatment episodes)*
- Blood clots in the veins in lungs, legs, liver, kidneys or at site of injection. Signs may include difficulty in breathing, red and painful swelling in the leg and abdominal pain.
- Lack of effect or decreased response to treatment.

► If you notice any of these serious side effects, get medical help immediately. Explain that you have been using NovoSeven.

Remind your doctor if you have a history of allergic reactions as you may need to be monitored more carefully. In most cases of blood clots, the patients were predisposed to blood clotting disorders.

Other rare side effects
(may affect up to 1 in 1,000 treatment episodes)
- Nausea (feeling sick)
- Headache
- Changes in some liver and blood tests.

Other uncommon side effects
(may affect up to 1 in 100 treatment episodes)
- Allergic skin reactions including rash, itching and hives
- Fever.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NovoSeven

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date that is stated on the carton. The expiry date refers to the last day of that month.
- Store powder and solvent below 25°C.
- Store powder and solvent protected from light.
- Do not freeze.
- Use NovoSeven at once after mixing the powder with the solvent to avoid infection. If you cannot use it immediately, after it has been mixed, you should store it in the vial with the vial adapter and syringe still attached in a refrigerator at 2°C to 8°C for no longer than 24 hours. Do not freeze the mixed NovoSeven solution and keep it protected from light. Do not store the solution without advice from your doctor or nurse.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NovoSeven contains
- The active substance is recombinant coagulation factor VIIa (activated eptacog alfa).
- The other ingredients in the powder are sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, hydrochloric acid, sodium hydroxide. The ingredients in the solvent are histidine, hydrochloric acid, sodium hydroxide, water for injections.

The powder for solution for injection contains: 1 mg/vial (corresponding to 50 KIU/vial), 2 mg/vial (corresponding to 100 KIU/vial), 5 mg/vial (corresponding to 250 KIU/vial) or 8 mg/vial (corresponding to 400 KIU/vial).
After reconstitution, 1 ml of the solution contains 1 mg eptacog alfa (activated).
1 KIU equals 1,000 IU (International Units).

What NovoSeven looks like and contents of the pack
The powder vial contains white powder and the pre-filled syringe contains a clear colourless solution. The reconstituted solution is colourless. Do not use the reconstituted solution if you notice particles in it or if it is discoloured.

Each NovoSeven pack contains:
- 1 vial with white powder for solution for injection
- 1 vial adapter
- 1 pre-filled syringe with solvent for reconstitution
- 1 plunger rod

Pack sizes: 1 mg (50 KIU), 2 mg (100 KIU), 5 mg (250 KIU) and 8 mg (400 KIU).

Please refer to outer packaging for present pack size.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in 01/2023

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

Instructions on how to use NovoSeven

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NOVOSEVEN

NovoSeven is supplied as a powder. Before injection (administration) it must be reconstituted with the solvent supplied in the syringe. The solvent is a histidine solution. The reconstituted NovoSeven must be injected into your vein (intravenous injection). The equipment in this package is designed to reconstitute and inject NovoSeven.

You will also need an administration set (tubing and butterfly needle, sterile alcohol swabs, gauze pads and plasters). These devices are not included in the NovoSeven package.

Do not use the equipment without proper training from your doctor or nurse.

Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medication directly into the vein, it is important **to use a clean and germ free (aseptic) technique**. Improper technique can introduce germs that can infect the blood.

Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it is expired. Use a new package instead. The expiry date is printed after 'EXP' on the outer carton, on the vial, on the vial adapter and on the pre-filled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

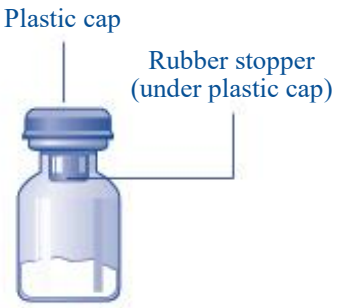
Contents

The package contains:

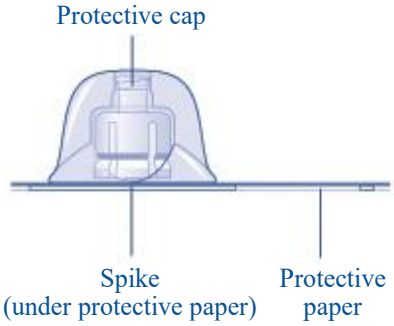
- 1 vial with NovoSeven powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

Overview

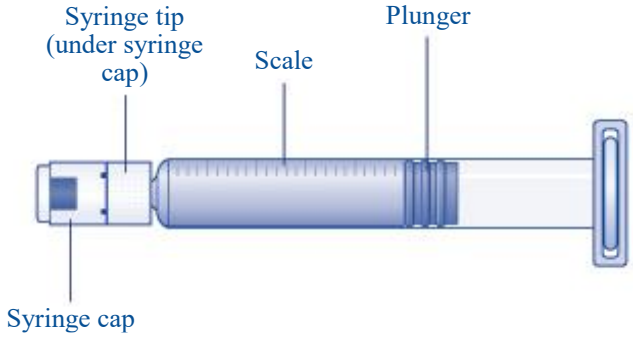
Vial with NovoSeven powder



Vial adapter

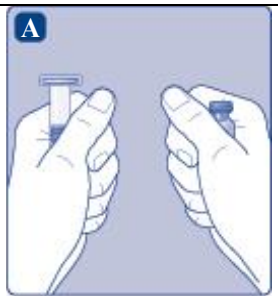


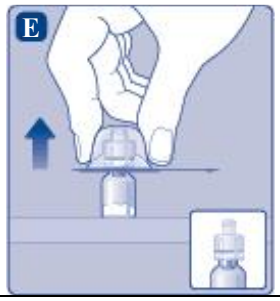
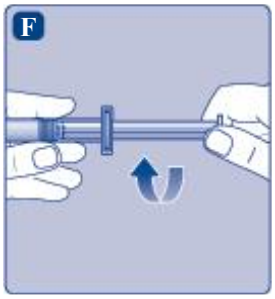
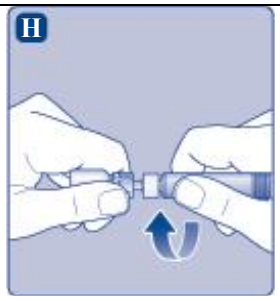
Pre-filled syringe with solvent

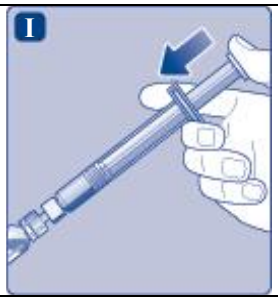


Plunger rod

1. Prepare the vial and the syringe	

• **Take out the number of NovoSeven packages you need.** • **Check the expiry date.** • **Check the name, strength and colour** of the package, to make sure it contains the correct product. • **Wash your hands** and dry them properly using a clean towel or air dry. • Take the vial, the vial adapter and the pre-filled syringe out of the carton. **Leave the plunger rod untouched in the carton.** • **Bring the vial and the pre-filled syringe to room temperature** (not above 37°C). You can do this by holding them in your hands until they feel as warm as your hands. • **Do not use any other way to warm** the vial and pre-filled syringe.	
• **Remove the plastic cap** from the vial. **If the plastic cap is loose or missing, do not use the vial.** • **Wipe the rubber stopper** with a sterile alcohol swab and allow it to air dry for a few seconds before use to ensure that it is as germ free as possible. • **Do not touch the rubber stopper with your fingers as this can transfer germs.**	
2. Attach the vial adapter • **Remove the protective paper** from the vial adapter. **If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.** **Do not take the vial adapter out of the protective cap with your fingers.** If you touch the spike on the vial adapter germs from your fingers can be transferred.	
• **Place the vial on a flat and solid surface.** • **Turn over the protective cap,** and snap the vial adapter onto the vial. **Once attached, do not remove the vial adapter from the vial.**	

	
• Lightly **squeeze the protective cap** with your thumb and index finger as shown. **Remove the protective cap** from the vial adapter. **Do not lift the vial adapter from the vial** when removing the protective cap.	
3. Attach the plunger rod and the syringe • Grasp the plunger rod by the wide top-end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers can be transferred. **Immediately** connect the plunger rod to the syringe by turning it 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 you touch the syringe tip, germs from your fingers can be transferred. **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.	
4. Reconstitute the powder with the solvent • **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.** • **Check the reconstituted solution.** It must be colourless. **If you notice visible particles or discolouration, do not use it.** Use a new package instead.	

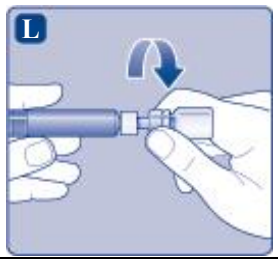
Use the reconstituted NovoSeven at once to avoid infections.

If you cannot use it at once, see section 5 *How to store NovoSeven* on the other side of this leaflet. Do not store the reconstituted solution without advice from your doctor or nurse.

(I)
If your dose requires more than one vial, repeat steps **A** to **J** with additional vials, vial adapters and pre-filled syringes until you have reached your required dose.

• **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 reconstituted solution into the syringe. • In case you only need part of the reconstituted solution, use the scale on the syringe to see how much of the solution you withdraw, as instructed by your doctor or nurse. • If, at any point, there is too much air in the syringe, inject the air back into the vial. • 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.	

- **Unscrew the vial adapter** with the vial.
- **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers can be transferred.



Injecting NovoSeven with pre-filled syringe via needleless connectors for intravenous (IV) catheters

Caution: The pre-filled syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the pre-filled syringe. This incompatibility may prevent administration of the drug and/or result in damage to the needleless connector.

Follow the instructions for use for the needleless connector. Administration through a needleless connector may require withdrawal of the reconstituted solution into a standard 10 ml sterile luer-lock plastic syringe. This should be done right after step J.

5. Inject the reconstituted solution

NovoSeven is now ready to inject into your vein.

- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 2 to 5 minutes.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:

- Use a clean and germ free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 ml plastic syringe for withdrawal of the reconstituted solution.
- If the CVAD line needs to be flushed before or after NovoSeven injection, use sodium chloride 9 mg/ml solution for injection.

Disposal

- **After injection, safely dispose** of the syringe with the administration set, the vial with the vial adapter, any unused NovoSeven and other waste materials as instructed by your doctor or nurse.
- Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.

Do not reuse the equipment.