

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 1.2 mg (60 KIU) – powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven is presented as powder and solvent for solution for injection containing 1.2 mg eptacog alfa (activated) per vial (corresponds to 60 KIU/vial).
1 KIU equals 1,000 IU (International Units).

Eptacog alfa (activated) is recombinant coagulation factor VIIa with a molecular mass of approximately 50,000 Daltons produced by genetic engineering from baby hamster kidney cells (BHK Cells).

After reconstitution the product contains 0.6 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.

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 antibodies to GP IIb – IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 NovoSeven, 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 NovoSeven.

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 potential 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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.

Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and NovoSeven 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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)
Not known	

	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous)
Not known	– Pruritus and urticaria
	– Flushing
	– Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased*
	– Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products
	– Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
<p>Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.</p>	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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.

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.

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.

5.2 Pharmacokinetic properties

Healthy subjects

Distribution, elimination and linearity

Using the FVII clotting assay, the pharmacokinetics of NovoSeven 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 NovoSeven 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 NovoSeven 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 NovoSeven, 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.

5.3 Preclinical safety data

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

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
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

Solvent

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 is 3 years for the product packed for sale.

After reconstitution, chemical and physical stability has been demonstrated for 24 hours at 25°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 would normally 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.

6.4 Special precautions for storage

- Store NovoSeven in a refrigerator (2°C – 8°C)
- Store in original package in order to protect from light
- Do not freeze to prevent damage to the solvent vial.

6.5 Nature and contents of container

Vials for NovoSeven:

Glass closed with a bromobutyl rubber stopper covered with an aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Vials for solvent:

Glass closed with a bromobutyl rubber disc with teflon, covered with an aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Syringe for reconstitution and administration:

The sterile disposable syringe is made of polypropylene.

The NovoSeven package contains:

- 1 vial (2 ml) with white powder (NovoSeven) for solution for injection
- 1 vial (2 ml) with solvent (Water for injections) for reconstitution
- 1 sterile vial adapter for reconstitution
- 1 sterile disposable syringe for reconstitution and administration
- 1 sterile infusion set for administration
- 2 alcohol swabs for cleansing the rubber stoppers on the vials
- Package leaflet with instructions for use.

6.6 Special precautions for disposal and other handling

Always use an aseptic technique.

Reconstitution

- Bring the NovoSeven powder and water vials to room temperature (but not above 37°C). You can do this by holding them in your hands. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with the alcohol swabs and allow them to dry before use.
- Remove the protective paper from the vial adapter without taking the vial adapter out of the protective cap. Attach the vial adapter to the solvent vial. Take care not to touch the spike on the vial adapter.
Once attached, remove the protective cap from the vial adapter.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).
- Screw the syringe tightly onto the vial adapter on the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the water vial upside down and pull the plunger to draw the water into the syringe.
- Remove the empty water vial by tipping the syringe with the vial adapter.
- Click the vial adapter, still attached to the syringe, onto the powder vial. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the water into the powder vial. Make sure not to aim the stream of water directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

NovoSeven reconstituted solution is colourless and should be inspected visually for particulate matter

and discolouration prior to administration.

The enclosed disposable syringe is compatible with the reconstituted preparation, but **do not** store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- Unscrew the vial adapter with the empty 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 syringe, vial adapter, vials, infusion set and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/96/006/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 2.4 mg (120 KIU) - powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven is presented as powder and solvent for solution for injection containing 2.4 mg eptacog alfa (activated) per vial (corresponds to 120 KIU/vial).
1 KIU equals 1,000 IU (International Units).

Eptacog alfa (activated) is recombinant coagulation factor VIIa with a molecular mass of approximately 50,000 Daltons produced by genetic engineering from baby hamster kidney cells (BHK Cells).

After reconstitution the product contains 0.6 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.

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 antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 NovoSeven, 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 NovoSeven.

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 potential 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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.

Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and NovoSeven 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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)

Not known	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria
Not known	– Flushing – Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased* – Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products – Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
<p>Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.</p>	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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.

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.

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.

5.2 Pharmacokinetic properties

Healthy subjects

Distribution, elimination and linearity

Using the FVII clotting assay, the pharmacokinetics of NovoSeven 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 NovoSeven 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 NovoSeven 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 NovoSeven, 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.

5.3 Preclinical safety data

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

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
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

Solvent

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 is 3 years for the product packed for sale.

After reconstitution, chemical and physical stability has been demonstrated for 24 hours at 25°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 would normally 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.

6.4 Special precautions for storage

- Store NovoSeven in a refrigerator (2°C – 8°C)
- Store in original package in order to protect from light
- Do not freeze to prevent damage to the solvent vial.

6.5 Nature and contents of container

Vials for NovoSeven:

Glass closed with a bromobutyl rubber stopper covered with an aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Vials for solvent:

Glass closed with a bromobutyl rubber disc with teflon, covered with an aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Syringe for reconstitution and administration:

The sterile disposable syringe is made of polypropylene.

The NovoSeven package contains:

- 1 vial (5 ml) with white powder (NovoSeven) for solution for injection
- 1 vial (5 ml) with solvent (Water for injections) for reconstitution
- 1 sterile vial adapter for reconstitution
- 1 sterile disposable syringe for reconstitution and administration
- 1 sterile infusion set for administration
- 2 alcohol swabs for cleansing the rubber stoppers on the vials
- Package leaflet with instructions for use.

6.6 Special precautions for disposal and other handling

Always use an aseptic technique.

Reconstitution

- Bring the NovoSeven powder and water vials to room temperature (but not above 37°C). You can do this by holding them in your hands. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with the alcohol swabs and allow them to dry before use.
- Remove the protective paper from the vial adapter without taking the vial adapter out of the protective cap. Attach the vial adapter to the solvent vial. Take care not to touch the spike on the vial adapter.
Once attached, remove the protective cap from the vial adapter.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).
- Screw the syringe tightly onto the vial adapter on the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the water vial upside down and pull the plunger to draw the water into the syringe.
- Remove the empty water vial by tipping the syringe with the vial adapter.
- Click the vial adapter, still attached to the syringe, onto the powder vial. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the water into the powder vial. Make sure not to aim the stream of water directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

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

The enclosed disposable syringe is compatible with the reconstituted preparation, but **do not** store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- Unscrew the vial adapter with the empty 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 syringe, vial adapter, vials, infusion set and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/96/006/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 4.8 mg (240 KIU) - powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven is presented as powder and solvent for solution for injection containing 4.8 mg eptacog alfa (activated) per vial (corresponds to 240 KIU/vial).
1 KIU equals 1,000 IU (International Units).

Eptacog alfa (activated) is recombinant coagulation factor VIIa with a molecular mass of approximately 50,000 Daltons produced by genetic engineering from baby hamster kidney cells (BHK Cells).

After reconstitution the product contains 0.6 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.

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 antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 NovoSeven, 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 NovoSeven.

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 potential 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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.

Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and NovoSeven 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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)

Not known	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria
Not known	– Flushing – Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased* – Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products – Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
<p>Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.</p>	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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.

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.

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.

5.2 Pharmacokinetic properties

Healthy subjects

Distribution, elimination and linearity

Using the FVII clotting assay, the pharmacokinetics of NovoSeven 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 NovoSeven 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 NovoSeven 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 NovoSeven, 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.

5.3 Preclinical safety data

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

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
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

Solvent

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 is 3 years for the product packed for sale.

After reconstitution, chemical and physical stability has been demonstrated for 24 hours at 25°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 would normally 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.

6.4 Special precautions for storage

- Store NovoSeven in a refrigerator (2°C – 8°C)
- Store in original package in order to protect from light
- Do not freeze to prevent damage to the solvent vial.

6.5 Nature and contents of container

Vials for NovoSeven:

Glass closed with a bromobutyl rubber stopper covered with an aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Vials for solvent:

Glass closed with a bromobutyl rubber disc with teflon, covered with an aluminium cap.

The closed vials are equipped with a tamper-evident snap-off cap which is made of polypropylene.

Syringe for reconstitution and administration:

The sterile disposable syringe is made of polypropylene.

The NovoSeven package contains:

- 1 vial (12 ml) with white powder (NovoSeven) for solution for injection
- 1 vial (12 ml) with solvent (Water for injections) for reconstitution
- 1 sterile vial adapter for reconstitution
- 1 sterile disposable syringe for reconstitution and administration
- 1 sterile infusion set for administration
- 2 alcohol swabs for cleansing the rubber stoppers on the vials
- Package leaflet with instructions for use.

6.6 Special precautions for disposal and other handling

Always use an aseptic technique.

Reconstitution

- Bring the NovoSeven powder and water vials to room temperature (but not above 37°C). You can do this by holding them in your hands. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with the alcohol swabs and allow them to dry before use.
- Remove the protective paper from the vial adapter without taking the vial adapter out of the protective cap. Attach the vial adapter to the solvent vial. Take care not to touch the spike on the vial adapter.
Once attached, remove the protective cap from the vial adapter.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).
- Screw the syringe tightly onto the vial adapter on the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the water vial upside down and pull the plunger to draw the water into the syringe.
- Remove the empty water vial by tipping the syringe with the vial adapter.
- Click the vial adapter, still attached to the syringe, onto the powder vial. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the water into the powder vial. Make sure not to aim the stream of water directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

NovoSeven reconstituted solution is colourless and should be inspected visually for particulate matter

and discolouration prior to administration.

The enclosed disposable syringe is compatible with the reconstituted preparation, but **do not** store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- Unscrew the vial adapter with the empty 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 syringe, vial adapter, vials, infusion set and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

EU/1/96/006/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 1996

Date of latest renewal: 23 February 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 1 mg (50 KIU) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven is presented as powder and solvent for solution for injection containing 1 mg eptacog alfa (activated) per vial (corresponds to 50 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) and 10 mg/ml sucrose 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 antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 potential 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, septicemia 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena

or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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

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.

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

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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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

Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)
Not known	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria
Not known	– Flushing – Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased* – Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products – Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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 $\mu\text{g}/\text{kg}$ 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.

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.

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.

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.

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.

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.

6.4 Special precautions for storage

- Store powder and solvent below 25°C.
- Store powder and solvent protected from light.
- Do not freeze to prevent damage to the solvent vial/pre-filled syringe.
- 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 either a vial or in a pre-filled syringe. Not all presentations may be marketed.

The NovoSeven package contains either

- 1 vial (2 ml) with white powder for solution for injection
- 1 vial (2 ml) with solvent for reconstitution

or

- 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

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 either a vial or in a pre-filled syringe. Not all presentations may be marketed. Handling procedures for both presentations are described below.

Powder in vial and solvent in vial:

Always use an aseptic technique.

Reconstitution

- NovoSeven powder and solvent vials should be at room temperature at reconstitution. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use. Use a disposable syringe of an appropriate size and a vial adapter, transfer needle (20 – 26G) or other suitable device.
- Attach the vial adapter to the solvent vial. If using a transfer needle, screw the transfer needle tightly onto the syringe.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).

- Screw the syringe tightly onto the vial adapter on the solvent vial. If using a transfer needle, insert the transfer needle into the rubber stopper of the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the solvent vial upside down. If using a transfer needle, make sure the transfer needle tip is in the solvent. Pull the plunger to draw the solvent into the syringe.
- Remove the empty solvent vial. If using a vial adapter, tip the syringe to remove it from the vial.
- Attach the syringe with the vial adapter or transfer needle to the powder vial. If using a transfer needle, make sure to penetrate the centre of the rubber stopper. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

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

Do not store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). If using a transfer needle, make sure the transfer needle tip is in the solution. Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- If using a vial adapter, unscrew the vial adapter with the empty vial. If using a transfer needle, remove the transfer needle from the vial, replace the transfer needle cap, and twist the transfer needle off the syringe.
- 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 syringe, vials and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/96/006/004
EU/1/96/006/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 1996

Date of latest renewal: 23 February 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 2 mg (100 KIU) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven is presented as powder and solvent for solution for injection containing 2 mg eptacog alfa (activated) per vial (corresponds to 100 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) and 10 mg/ml sucrose 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 antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 potential 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, septicemia 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena

or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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

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.

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

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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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

Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)
Not known	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria
Not known	– Flushing – Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased* – Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products – Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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 $\mu\text{g}/\text{kg}$ 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.

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.

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.

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.

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.

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.

6.4 Special precautions for storage

- Store powder and solvent below 25°C.
- Store powder and solvent protected from light.
- Do not freeze to prevent damage to the solvent vial/pre-filled syringe.
- 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 either a vial or in a pre-filled syringe. Not all presentations may be marketed.

The NovoSeven package contains either

- 1 vial (2 ml) with white powder for solution for injection
- 1 vial (2 ml) with solvent for reconstitution

or

- 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

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 either a vial or in a pre-filled syringe. Not all presentations may be marketed. Handling procedures for both presentations are described below.

Powder in vial and solvent in vial:

Always use an aseptic technique.

Reconstitution

- NovoSeven powder and solvent vials should be at room temperature at reconstitution. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use. Use a disposable syringe of an appropriate size and a vial adapter, transfer needle (20 – 26G) or other suitable device.
- Attach the vial adapter to the solvent vial. If using a transfer needle, screw the transfer needle tightly onto the syringe.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).

- Screw the syringe tightly onto the vial adapter on the solvent vial. If using a transfer needle, insert the transfer needle into the rubber stopper of the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the solvent vial upside down. If using a transfer needle, make sure the transfer needle tip is in the solvent. Pull the plunger to draw the solvent into the syringe.
- Remove the empty solvent vial. If using a vial adapter, tip the syringe to remove it from the vial.
- Attach the syringe with the vial adapter or transfer needle to the powder vial. If using a transfer needle, make sure to penetrate the centre of the rubber stopper. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

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

Do not store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). If using a transfer needle, make sure the transfer needle tip is in the solution. Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- If using a vial adapter, unscrew the vial adapter with the empty vial. If using a transfer needle, remove the transfer needle from the vial, replace the transfer needle cap, and twist the transfer needle off the syringe.
- 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 syringe, vials and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/96/006/005
EU/1/96/006/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 1996

Date of latest renewal: 23 February 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 5 mg (250 KIU) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NovoSeven is presented as powder and solvent for solution for injection containing 5 mg eptacog alfa (activated) per vial (corresponds to 250 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) and 10 mg/ml sucrose 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 antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 potential 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, septicemia 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena

or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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

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.

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

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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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

Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)
Not known	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria
Not known	– Flushing – Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased* – Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products – Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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 $\mu\text{g}/\text{kg}$ 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.

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.

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.

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.

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.

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.

6.4 Special precautions for storage

- Store powder and solvent below 25°C.
- Store powder and solvent protected from light.
- Do not freeze to prevent damage to the solvent vial/pre-filled syringe.
- 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 either a vial or in a pre-filled syringe. Not all presentations may be marketed.

The NovoSeven package contains either

- 1 vial (12 ml) with white powder for solution for injection
- 1 vial (12 ml) with solvent for reconstitution

or

- 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

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 either a vial or in a pre-filled syringe. Not all presentations may be marketed. Handling procedures for both presentations are described below.

Powder in vial and solvent in vial:

Always use an aseptic technique.

Reconstitution

- NovoSeven powder and solvent vials should be at room temperature at reconstitution. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use. Use a disposable syringe of an appropriate size and a vial adapter, transfer needle (20 – 26G) or other suitable device.
- Attach the vial adapter to the solvent vial. If using a transfer needle, screw the transfer needle tightly onto the syringe.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).

- Screw the syringe tightly onto the vial adapter on the solvent vial. If using a transfer needle, insert the transfer needle into the rubber stopper of the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the solvent vial upside down. If using a transfer needle, make sure the transfer needle tip is in the solvent. Pull the plunger to draw the solvent into the syringe.
- Remove the empty solvent vial. If using a vial adapter, tip the syringe to remove it from the vial.
- Attach the syringe with the vial adapter or transfer needle to the powder vial. If using a transfer needle, make sure to penetrate the centre of the rubber stopper. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

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

Do not store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). If using a transfer needle, make sure the transfer needle tip is in the solution. Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- If using a vial adapter, unscrew the vial adapter with the empty vial. If using a transfer needle, remove the transfer needle from the vial, replace the transfer needle cap, and twist the transfer needle off the syringe.
- 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 syringe, vials and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/96/006/006
EU/1/96/006/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 1996

Date of latest renewal: 23 February 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven 8 mg (400 KIU) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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) and 10 mg/ml sucrose 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 antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

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.

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.

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 potential 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 patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena

or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven should be weighed against the risk of these complications.

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).

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

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.

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

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 ($\geq 1/1,000$, $< 1/100$).

Tabulated summary of adverse reactions

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

<i>Blood and the lymphatic system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT (see section 4.4) – Coagulopathy
<i>Immune system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Hypersensitivity (see sections 4.3 and 4.4)
Not known	– Anaphylactic reaction
<i>Nervous system disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Headache
<i>Vascular disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	<ul style="list-style-type: none"> – 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

Uncommon ($\geq 1/1,000$, $< 1/100$)	– Venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia)
Not known	– Intracardiac thrombus
<i>Gastrointestinal disorders</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Nausea
<i>Skin and subcutaneous disorders</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Rash (including allergic dermatitis and rash erythematous) – Pruritus and urticaria
Not known	– Flushing – Angioedema
<i>General disorders and administration site conditions</i>	
Uncommon ($\geq 1/1,000$, $< 1/100$)	– Therapeutic response decreased* – Pyrexia
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Injection site reaction including injection site pain
<i>Investigations</i>	
Rare ($\geq 1/10,000$, $< 1/1,000$)	– Increased fibrin degradation products – Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.	

* 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 ($\geq 1/100$ 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 ($\geq 1/100$ 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.

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 $\mu\text{g}/\text{kg}$ 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.

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.

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.

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.

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.

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.

6.4 Special precautions for storage

- Store powder and solvent below 25°C.
- Store powder and solvent protected from light.
- Do not freeze to prevent damage to the solvent vial/pre-filled syringe.
- 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 either a vial or in a pre-filled syringe. Not all presentations may be marketed.

The NovoSeven package contains either

- 1 vial (12 ml) with white powder for solution for injection
- 1 vial (12 ml) with solvent for reconstitution

or

- 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

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 either a vial or in a pre-filled syringe. Not all presentations may be marketed. Handling procedures for both presentations are described below.

Powder in vial and solvent in vial:

Always use an aseptic technique.

Reconstitution

- NovoSeven powder and solvent vials should be at room temperature at reconstitution. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use. Use a disposable syringe of an appropriate size and a vial adapter, transfer needle (20 – 26G) or other suitable device.
- Attach the vial adapter to the solvent vial. If using a transfer needle, screw the transfer needle tightly onto the syringe.
- Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).

- Screw the syringe tightly onto the vial adapter on the solvent vial. If using a transfer needle, insert the transfer needle into the rubber stopper of the solvent vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.
- Hold the syringe with the solvent vial upside down. If using a transfer needle, make sure the transfer needle tip is in the solvent. Pull the plunger to draw the solvent into the syringe.
- Remove the empty solvent vial. If using a vial adapter, tip the syringe to remove it from the vial.
- Attach the syringe with the vial adapter or transfer needle to the powder vial. If using a transfer needle, make sure to penetrate the centre of the rubber stopper. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the NovoSeven powder as this will cause foaming.
- Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming.

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

Do not store reconstituted NovoSeven in plastic syringes.

It is recommended to use NovoSeven immediately after reconstitution.

Administration

- Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). If using a transfer needle, make sure the transfer needle tip is in the solution. Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.
- If using a vial adapter, unscrew the vial adapter with the empty vial. If using a transfer needle, remove the transfer needle from the vial, replace the transfer needle cap, and twist the transfer needle off the syringe.
- 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 syringe, vials and any unused product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/96/006/007
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: 23 February 2006

10. DATE OF REVISION OF THE TEXT

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 (PSUR)**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, at launch, all physicians who are expected to prescribe/use NovoSeven are provided with an educational pack containing the following:

- Physician information pack

- Patient information pack

Both information packs are to be used as part of an educational plan provided to minimise risk of medication errors that may be associated with the change in concentration of the new NovoSeven formulation.

The physician information pack should contain the following:

- Summary leaflet of the product features and reconstitution guide, including highlighted changes that have been made for the new formulation of NovoSeven.
- Educational slide kit
- Dosing reference card
- Question & Answer booklet
- Patient information pack
- Letter to healthcare professionals.

The physician information should contain the following key elements:

- Clear demarcation of the new formulation of NovoSeven from original NovoSeven, with clear descriptions of any differences in the vial sizes, colour codes and dosing and reconstitution instructions
- Clear information about their difference in concentration.
- Information about the potential safety risks of errors in dosing calculation resulting from the confusion between the two formulations and its possible clinical consequences (e.g. potential for thrombotic risk if overdose).
- Encouragement to report medications errors and their causes and consequences.

The patient information pack to be used by healthcare professionals in the education of the patients should contain the same above described key elements.

The Marketing Authorisation Holder must implement this educational plan nationally, prior to marketing, and as agreed with the competent authorities in the Member States.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven
1.2 mg (60 KIU)
Powder and solvent for solution for injection
Eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

The reconstituted product contains
Eptacog alfa (activated) (Recombinant coagulation factor VIIa) 0.6 mg/ml

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Contents:
1 vial freeze-dried eptacog alfa (activated) 1.2 mg and excipients
1 vial 2.2 ml water for injections
1 injection syringe, 3 ml
1 vial adapter for reconstitution
1 infusion set
2 alcohol swabs
Package leaflet with instructions for use

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous, 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 in a refrigerator
Do not freeze to prevent damage to the solvent vial
Store in original package in order to protect 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/1/96/006/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Inner carton text

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven
1.2 mg (60 KIU)
Powder and solvent for solution for injection

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven
1.2 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

1.2 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for Solvent vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven
2.4 mg (120 KIU)
Powder and solvent for solution for injection
Eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

The reconstituted product contains
Eptacog alfa (activated) (Recombinant coagulation factor VIIa) 0.6 mg/ml

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Contents:

1 vial freeze-dried eptacog alfa (activated) 2.4 mg and excipients
1 vial 4.3 ml water for injections
1 injection syringe, 6 ml
1 vial adapter for reconstitution
1 infusion set
2 alcohol swabs
Package leaflet with instructions for use

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous, 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 in a refrigerator
Do not freeze to prevent damage to the solvent vial
Store in original package in order to protect 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/1/96/006/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Inner carton text

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven
2.4 mg (120 KIU)
Powder and solvent for solution for injection

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven
2.4 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

2.4 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for Solvent vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4.3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton text

1. NAME OF THE MEDICINAL PRODUCT

NovoSeven
4.8 mg (240 KIU)
Powder and solvent for solution for injection
Eptacog alfa (activated)

2. STATEMENT OF ACTIVE SUBSTANCE

The reconstituted product contains
Eptacog alfa (activated) (Recombinant coagulation factor VIIa) 0.6 mg/ml

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Contents:

1 vial freeze-dried eptacog alfa (activated) 4.8 mg and excipients
1 vial 8.5 ml water for injections
1 injection syringe, 12 ml
1 vial adapter for reconstitution
1 infusion set
2 alcohol swabs
Package leaflet with instructions for use

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous, 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 in a refrigerator
Do not freeze to prevent damage to the solvent vial
Store in original package in order to protect 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/1/96/006/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Inner carton text

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven
4.8 mg (240 KIU)
Powder and solvent for solution for injection

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for powder vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NovoSeven
4.8 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

4.8 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for Solvent vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8.5 ml

6. OTHER

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

See package leaflet for further information on sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:

1 vial of powder
1 vial of solvent

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 to prevent damage to the solvent vial
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/1/96/006/004

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

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

See package leaflet for further information on sucrose

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 to prevent damage to the pre-filled syringe
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

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 Solvent vial

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

1.1 ml

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

See package leaflet for further information on sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:

1 vial of powder
1 vial of solvent

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 to prevent damage to the solvent vial
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/1/96/006/005

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

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

See package leaflet for further information on sucrose

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 to prevent damage to the pre-filled syringe
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

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 Solvent vial

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

2.1 ml

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

See package leaflet for further information on sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:

1 vial of powder
1 vial of solvent

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 to prevent damage to the solvent vial
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/1/96/006/006

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

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

See package leaflet for further information on sucrose

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 to prevent damage to the pre-filled syringe
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

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 Solvent vial

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

5.2 ml

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

See package leaflet for further information on sucrose

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack contains:

1 vial of powder
1 vial of solvent

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 to prevent damage to the solvent vial
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/1/96/006/007

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

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

See package leaflet for further information on sucrose

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 to prevent damage to the pre-filled syringe
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

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 Solvent vial

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

8.1 ml

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 1.2 mg (60 KIU) powder and solvent for solution for injection
NovoSeven 2.4 mg (120 KIU) powder and solvent for solution for injection
NovoSeven 4.8 mg (240 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
2. What you need to know before you use NovoSeven
3. How to use NovoSeven
4. Possible side effects
5. How to store NovoSeven
6. Contents of the pack and other information

Overleaf: NovoSeven user instructions

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.

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.

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 doses*)

- 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 doses*)

- 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 doses*)

- Nausea (feeling sick)
- Headache
- Changes in some liver and blood tests.

Other uncommon side effects

(*may affect up to 1 in 100 doses*)

- 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.
- Store NovoSeven in a refrigerator (2°C - 8°C).
- Store in original package in order to protect from light.
- Do not freeze, to prevent damage to the solvent vial.
- 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.
- 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 syringe still attached in a refrigerator at 2°C to 8°C for no longer than 24 hours. 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, glycyglycine, polysorbate 80, mannitol, hydrochloric acid and sodium hydroxide. The solvent is water for injections.

The powder for solution for injection contains: 1.2 mg/vial (corresponding to 60 KIU/vial), 2.4 mg/vial (corresponding to 120 KIU/vial) or 4.8 mg/vial (corresponding to 240 KIU/vial). After reconstitution, 1 ml of the solution contains 0.6 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 water vial contains a clear colourless solution. The reconstituted solution for injection is colourless. Do not use the reconstituted solution if particle formation or discolouration is noticed.

Each NovoSeven pack contains:

- 1 vial with white powder (NovoSeven) for solution for injection
- 1 vial with water (water for injections) for reconstitution
- 1 sterile vial adapter for reconstitution
- 1 sterile disposable syringe for reconstitution and administration
- 1 sterile infusion set
- 2 alcohol swabs.

Pack sizes: 1.2 mg (60 KIU), 2.4 mg (120 KIU) and 4.8 mg (240 KIU). Please refer to outer packaging for present pack size.

Marketing Authorisation Holder and Manufacturer

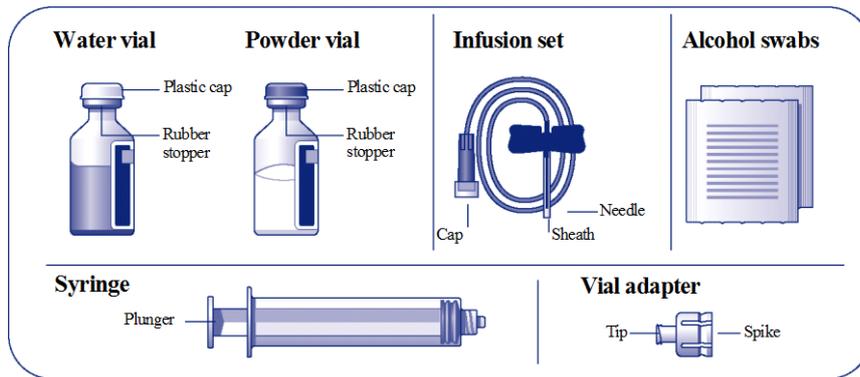
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

This leaflet was last revised in

Other sources of information

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

NOVOSEVEN USER INSTRUCTIONS



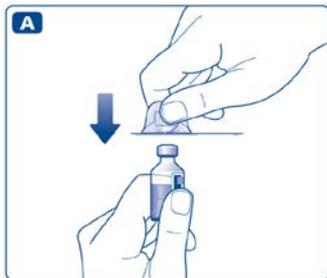
Preparing the solution

Wash your hands. Bring the NovoSeven powder and water vials to room temperature (but not above 37°C). You can do this by holding them in your hands. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with the alcohol swabs and allow them to dry before use.

A

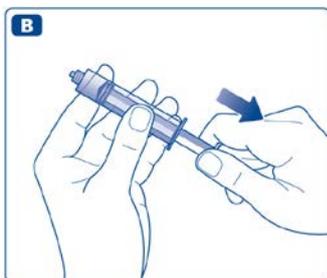
Remove the protective paper from the vial adapter without taking the vial adapter out of the protective cap. Attach the vial adapter to the water vial. Take care not to touch the spike on the vial adapter.

Once attached, remove the protective cap from the vial adapter.



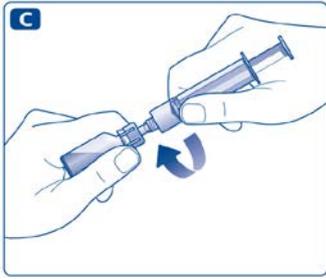
B

Pull the plunger to draw in a volume of air that is equal to the amount of water in the water vial (ml equals cc on the syringe).



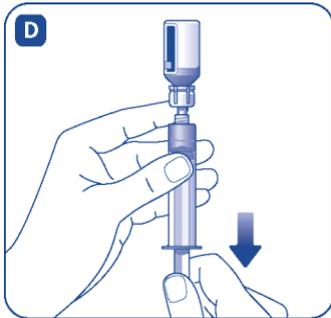
C

Screw the syringe tightly onto the vial adapter on the water vial. Inject air into the vial by pushing the plunger until you feel a clear resistance.



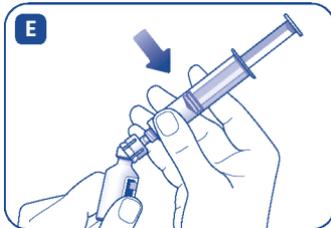
D

Hold the syringe with the water vial upside down and pull the plunger to draw the water into the syringe.



E

Remove the empty water vial by tipping the syringe with the vial adapter.



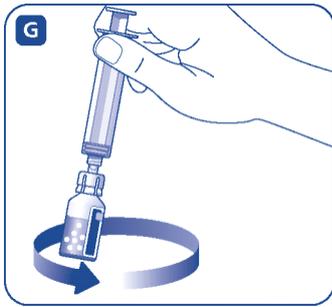
F

Click the vial adapter, still attached to the syringe, onto the powder vial. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the water into the powder vial. Make sure not to aim the stream of water directly at the NovoSeven powder as this will cause foaming.



G

Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. Check the solution for visible particles and discoloration. If you notice either, do not use it.

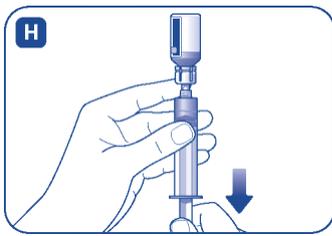


Although NovoSeven will be stable for 24 hours after it has been mixed, you should use it at once to avoid infection. If you do not use it immediately after mixing, you should store the vial with the syringe still attached in a refrigerator at 2°C to 8°C for no longer than 24 hours. Do not store the solution without your doctor's advice.

Injecting the solution

H

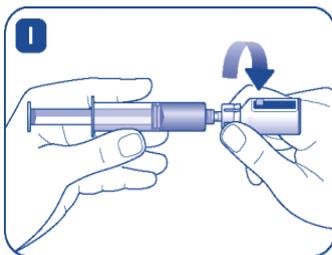
Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.



I

Unscrew the vial adapter with the empty vial.

NovoSeven is now ready for injection. Follow the injection procedure as instructed by your healthcare professional.



J

Safely dispose of the syringe, vial adapter, vials, infusion set and any unused product as instructed by your healthcare professional.



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
2. What you need to know before you use NovoSeven
3. How to use NovoSeven
4. Possible side effects
5. How to store NovoSeven
6. Contents of the pack and other information

Overleaf: NovoSeven user instructions

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.

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 sucrose

NovoSeven contains the sugar sucrose which consists of fructose and glucose. If you have been told by your doctor that you are intolerant to sucrose, fructose or glucose, or that you cannot absorb them properly, contact your doctor before taking NovoSeven.

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 doses*)

- 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 doses*)

- 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 doses*)

- Nausea (feeling sick)
- Headache
- Changes in some liver and blood tests.

Other uncommon side effects

(*may affect up to 1 in 100 doses*)

- 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, to prevent damage to the solvent vial.
- 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 solvent vial 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 with solvent for reconstitution

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**Other sources of information**

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

NOVOSEVEN USER INSTRUCTIONS

Solvent vial



Powder vial

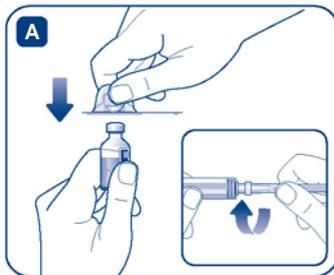


Preparing the solution

Wash your hands. NovoSeven powder and solvent vials should be at room temperature at reconstitution. Remove the plastic caps from the two vials. If the caps are loose or missing, do not use the vials. Clean the rubber stoppers on the vials with alcohol swabs and allow them to dry before use. Use a disposable syringe of an appropriate size and a vial adapter, transfer needle (20 – 26G) or other suitable device.

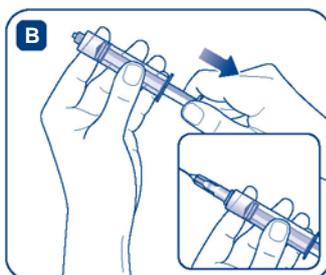
A

Remove the protective paper from the vial adapter without taking it out of the protective cap. Attach the vial adapter to the solvent vial. Once attached, remove the protective cap. Take care not to touch the spike on the vial adapter. If using a transfer needle, remove transfer needle from the packaging without taking it out of the protective cap. Screw the transfer needle tightly onto the syringe.



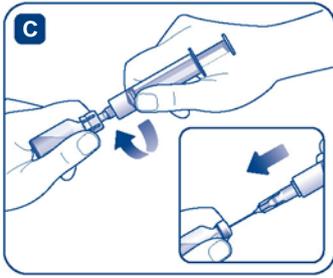
B

Pull the plunger to draw in a volume of air that is equal to the amount of solvent in the solvent vial (ml equals cc on the syringe).

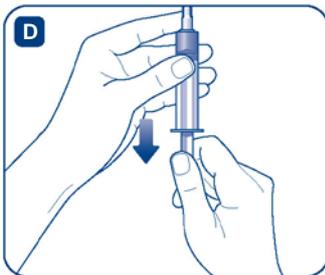


C

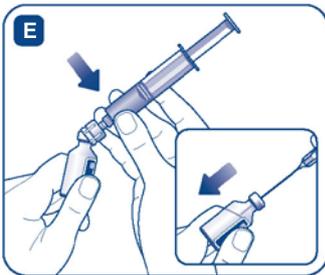
Screw the syringe tightly onto the vial adapter on the solvent vial. If using a transfer needle, remove the protective cap and insert the transfer needle into the rubber stopper of the solvent vial. Take care not to touch the end of the transfer needle. Inject air into the vial by pushing the plunger until you feel a clear resistance.

**D**

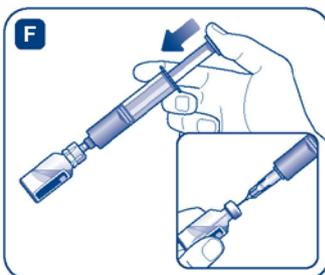
Hold the syringe with the solvent vial upside down. If you are using a transfer needle, make sure that the transfer needle tip is in the solvent. Pull the plunger to draw the solvent into the syringe.

**E**

Remove the empty solvent vial. If you use a vial adapter, tip the syringe to remove it from the vial.

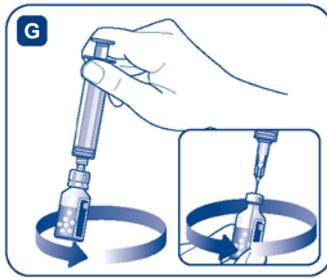
**F**

Attach the syringe with vial adapter or transfer needle to the powder vial. If you use a transfer needle, make sure to penetrate the centre of the rubber stopper. Hold the syringe slightly tilted with the vial facing downwards. Push the plunger slowly to inject the solvent into the powder vial. Make sure not to aim the stream of solvent directly at the NovoSeven powder as this will cause foaming.

**G**

Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. Check the solution for visible particles and discolouration. If you notice either, do not use it. NovoSeven reconstituted product is a clear, colourless solution. Keep the vial adapter or transfer

needle attached to the vial.

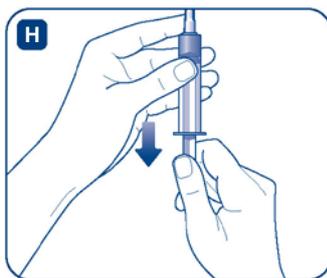


Although NovoSeven will be stable for 24 hours after it has been mixed, you should use it at once to avoid infection. If you do not use it immediately after mixing, you should store the vial with the syringe still attached in a refrigerator at 2°C to 8°C for no longer than 24 hours. Do not store the solution without your doctor's advice.

Injecting the solution

H

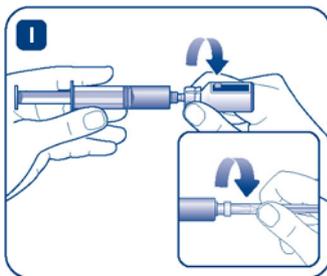
Ensure that the plunger is pushed all the way in before turning the syringe upside down (it may have been pushed out by the pressure in the syringe). If you use a transfer needle, make sure that the transfer needle tip is in the solution. Hold the syringe with the vial upside down and pull the plunger to draw all the solution into the syringe.



I

If you use a vial adapter, unscrew the vial adapter with the empty vial. If you use a transfer needle, remove the transfer needle from the vial, replace the transfer needle cap, and twist the transfer needle off the syringe.

NovoSeven is now ready for injection. Follow the injection procedure as instructed by your healthcare professional.



J

Safely dispose of the syringe, vials, any unused product and other waste materials as instructed by your healthcare professional.



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
2. What you need to know before you use NovoSeven
3. How to use NovoSeven
4. Possible side effects
5. How to store NovoSeven
6. Contents of the pack and other information

Overleaf: Instructions on how to use NovoSeven

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.

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 sucrose

NovoSeven contains the sugar sucrose which consists of fructose and glucose. If you have been told by your doctor that you are intolerant to sucrose, fructose or glucose, or that you cannot absorb them properly, contact your doctor before taking NovoSeven.

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 doses*)

- 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 doses*)

- 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 doses*)

- Nausea (feeling sick)
- Headache
- Changes in some liver and blood tests.

Other uncommon side effects

(*may affect up to 1 in 100 doses*)

- 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, to prevent damage to the pre-filled syringe.
- 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

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 infusion 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.

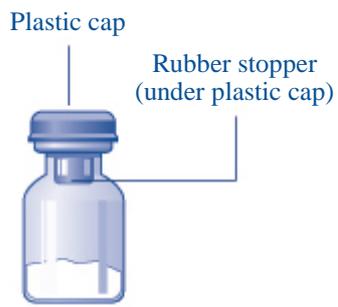
Contents

The package contains:

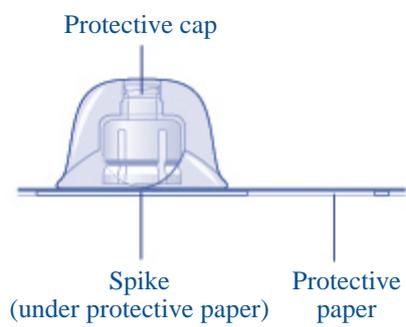
- 1 vial with NovoSeven powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

Overview

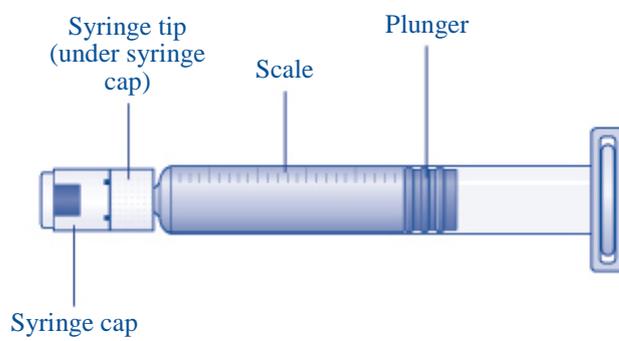
Vial with NovoSeven powder



Vial adapter



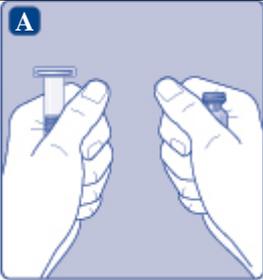
Pre-filled syringe with solvent

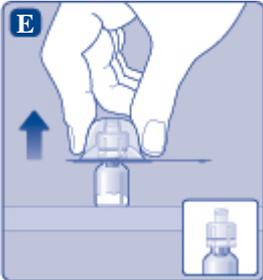
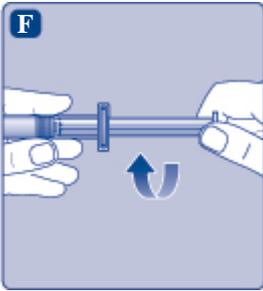
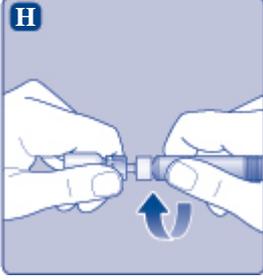


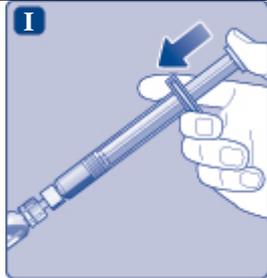
Plunger rod



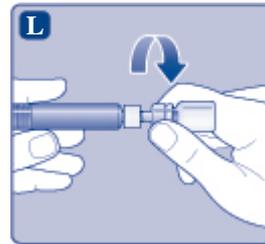
1. Prepare the vial and the syringe

<ul style="list-style-type: none"> • 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. 	
<ul style="list-style-type: none"> • 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. 	
<p>2. Attach the vial adapter</p> <ul style="list-style-type: none"> • Remove the protective paper from the vial adapter. <p>If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.</p> <p>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.</p>	
<ul style="list-style-type: none"> • Place the vial on a flat and solid surface. • Turn over the protective cap, and snap the vial adapter onto the vial. <p>Once attached, do not remove the vial adapter from the vial.</p>	

	
<ul style="list-style-type: none"> 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. 	
<p>3. Attach the plunger rod and the syringe</p> <ul style="list-style-type: none"> 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. 	
<ul style="list-style-type: none"> 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. 	
<ul style="list-style-type: none"> Screw the pre-filled syringe securely onto the vial adapter until resistance is felt. 	
<p>4. Reconstitute the powder with the solvent</p> <ul style="list-style-type: none"> Hold the pre-filled syringe slightly tilted with the vial pointing downwards. Push the plunger rod to inject all the solvent into the vial. 	

	
<ul style="list-style-type: none"> • 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. 	
<p>Use the reconstituted NovoSeven at once to avoid infections.</p> <p>If you cannot use it at once, see section 5 <i>How to store NovoSeven</i> on the other side of this leaflet. Do not store the reconstituted solution without advice from your doctor or nurse.</p> <p>(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.</p>	
<ul style="list-style-type: none"> • 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.

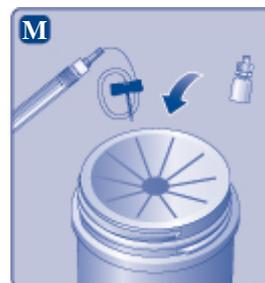
- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 2 to 5 minutes.

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 infusion 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.