**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.

**Dosage**

**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.

**Dosing in children**

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

**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 90μg per kg body weight administered at three-hour intervals.

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1 mg, 2 mg and 5 mg powder and solvent for solution for injection

**Qualitative and quantitative composition**

epptacog alfa (activated) 1 mg/vial (corresponds to 50 KIU/vial), 1 mg/ml after reconstitution
eptacog alfa (activated) 2 mg/vial (corresponds to 100 KIU/vial), 1 mg/ml after reconstitution
eptacog alfa (activated) 5 mg/vial (corresponds to 250 KIU/vial), 1 mg/ml after reconstitution
1 KIU equals 1000 IU (International Units)
eptacog alfa (activated) is recombinant coagulation factor VIIa (rFVIIa) with a molecular mass of approximately 50,000 Dalton produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology.

**Excipients:**

After reconstitution 1 ml solution contains 10 mg sucrose.

For a full list of excipients, see List of excipients.

**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.

**Clinical particulars**

**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 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.

**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.
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 the home therapy should not exceed 24 hours.

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 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.

**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 are the first line treatment for Glanzmann’s thrombasthenia.

**Method of administration**

Reconstitute the solution as described under NovoSeven® user instructions and administer 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 correla-
tion has been demonstrated between PT and aPTT and clinical efficacy of rFVIIa.

**Contraindications**

Hypersensitivity to the active substance, or to any of the excipients, or to mouse, hamster or bovine protein.

**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 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 following major surgery, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with NovoSeven® 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. The risk of thrombosis in factor VII deficient patients treated with NovoSeven® is unknown.

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

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.

**Pregnancy and lactation**

**Pregnancy**

As a precautionary measure it is preferable to avoid the 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, parturi-
**Nervous system disorders**  
Rare (>1/10,000, <1/1,000)  
Headache  

**Vascular disorders**  
Rare (>1/10,000, <1/1,000)  
Arterial thromboembolic events: (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia)  
Uncommon (>1/1,000, <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)  

**Gastrointestinal disorders**  
Rare (>1/10,000, <1/1,000)  
Nausea  

**Skin and subcutaneous disorders**  
Uncommon (>1/1,000, <1/100)  
Rash (including allergic dermatitis and rash erythematous)  
Pruritus and urticaria  

**General disorders and administration site conditions**  
Uncommon (>1/1,000, <1/100)  
Therapeutic response decreased*  
Pyrexia  

**Investigations**  
Rare (>1/10,000, <1/1,000)  
Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin.

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**Undesirable effects**  
Clinical trials conducted in 484 patients (including 4297 treatment episodes) with haemophilia A and B, acquired haemophilia, factor VII deficiency or Glanzmann’s thrombasthenia have shown that adverse drug reactions are common (≥1/100 to <1/10). As the total number of treatment episodes is below 10,000, the lowest possible frequency of adverse drug reactions that can be assigned is rare (>1/10,000, <1/1,000).  
The most frequent adverse drug reactions are pyrexia and rash (uncommon: >1/1,000, <1/100), and the most serious adverse drug reactions are thromboembolic events.  
The frequencies of both serious and non-serious adverse drug reactions are listed by system organ classes below.

### Blood and lymphatic system disorders  
Rare (>1/10,000, <1/1,000)  
Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and AT-III, see Special warnings and precautions for use Coagulopathy

### Immune system disorders  
Rare (>1/10,000, <1/1,000)  
Hypersensitivity, see Contraindications and Special warnings and precautions for use

Not known

Anaphylactic reaction

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**Lactation**  
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.

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

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**ACTIONS**

- **Preclinical safety data.**
- **Lactation**
- **Investigations**

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

**Blood and lymphatic system disorders**

Rare (>1/10,000, <1/1,000)  
Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and AT-III, see Special warnings and precautions for use Coagulopathy

**Immune system disorders**

Rare (>1/10,000, <1/1,000)  
Hypersensitivity, see Contraindications and Special warnings and precautions for use

Not known

Anaphylactic reaction
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 Dosage.

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

When NovoSeven® is administered to patients outside approved indications, arterial thromboembolic events are common (≥1/100 to <1/10). A higher risk of arterial thromboembolic adverse events (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® is not recommended.

Thromboembolic events may lead to cardiac arrest. There have been no confirmed reports of antibodies against NovoSeven® or FVII in patients with haemophilia A or B.

**Patients with Factor VII deficiency**

Formation of antibodies against NovoSeven® and FVII is the only adverse drug reaction reported in these clinical trials of patients with factor VII deficiency exposed to NovoSeven® (frequency: common (≥1/100 to <1/10)). In two out of five patients with reported antibody formation against NovoSeven® and FVII, reported in clinical trials and post-marketing, 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 *Special warnings and precautions for use*.

**Overdose**

Dose limiting toxicities of NovoSeven® have not been investigated in clinical trials. A few cases of overdose have been reported in patients with haemophilia. The only complication reported in connection with an overdose was a slight transient increase in blood pressure in a 16 year-old patient receiving 24 mg rFVIIa instead of 5.5 mg.

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

In patients with factor VII deficiency, where the recommended dose is 15-30 μg/kg rFVIIa, one episode of overdose has been associated with a thrombotic event (occipital stroke) in an elderly (>80 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.

**Pharmacological properties**

**Pharmacodynamic properties**

Pharmacotherapeutic group: Blood Coagulation factors, ATC code: B02BD08

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, localised to the site of injury, independent-
ly of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independently of tissue factor.

Accordingly, the pharmacodynamic effect of factor VIIa gives rise to an increased local formation of factor Xa, thrombin and fibrin.

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

**Pharmacokinetic properties**

**Healthy subjects**

Using the FVII clotting assay, the pharmacokinetics of NovoSeven® were investigated in 35 healthy Caucasian and Japanese subjects in a doseescalation study. Subjects were stratified according to sex and ethnic group and dosed with 40, 80 and 160 μg NovoSeven® per kg body weight and/or placebo (3 doses each). The pharmacokinetic profiles indicated dose proportionality. 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, and the mean terminal half-life ranged from 3.9 to 6.0 hours.

**Haemophilia A and B with inhibitors**

Using the FVIIa assay, the pharmacokinetic properties of NovoSeven® were studied in 12 paediatric (2-12 years) and five adult patients in non-bleeding state. 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). The 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. Mean volume of distribution at steady state was 196 mL/kg in paediatric patients versus 159 mL/kg in adults. Clearance appears related with age, therefore in younger patients clearance may be increased by more than 50%.

**Factor VII deficiency**

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: total body clearance (70.8-79.1 ml/h×kg), volume of distribution at steady state (280-290 ml/kg), mean residence time (3.75-3.80 h), and half-life (2.82-3.11 h). The mean in vivo plasma recovery was approximately 20%.

**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.

**Preclinical safety data**

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

**Pharmaceutical particulars**

**List of excipients**

**Powder**

Sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate 80, mannitol, sucrose, methionine, hydrochloric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment).

**Solvent**

Histidine, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.

**Incompatibilities**

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

**Shelf life**

After reconstitution, chemical and physical stability have 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.

**Special precautions for storage**

– Store powder and solvent below 25°C
– Store powder and solvent protected from light
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 needle, remove needle from the packaging without taking it out of the protective cap.

Screw the 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 needle, remove the protective cap and insert the needle into the rubber stopper of the solvent vial. Take care not to touch the end of the 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 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 bits and discoloration. If you notice either, do not use it.

NovoSeven® reconstituted product is a clear, colourless solution. Keep the vial adapter or 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-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 needle cap, and twist the 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.

*Please go to www.novonordisk.com for more information.*