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

eptacog alfa (activated) 1.2 mg/vial (corresponds to 60 KIU/vial)
1 KIU equals 1000 IU (International Units)

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

After reconstitution 1 ml solution contains 0.6 mg eptacog alfa (activated).

For a 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 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

Dosage

Haemophilia A or B with inhibitors or acquired haemophilia

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.

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 ambulatory treatment)
Early intervention in the ambulatory treatment setting with a dose of 90 µg per kg body weight has been efficacious in treating mild to moderate joint, muscle and mucocutaneous bleeds. One to three doses were administered at three-hour intervals to achieve haemostasis and one additional dose was given to maintain haemostasis. The duration of the ambulatory treatment should not exceed 24 hours.

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.

Factor VII deficiency

Dose, dose range and dose interval:
The recommended dose range for treatment of bleeding episodes 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.

Administration

Reconstitute the preparation as described under 6.6 and administer as an intravenous bolus injection over 2-5 minutes.

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

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

Known hypersensitivity to the active substance, the excipients, or to mouse, hamster or bovine protein may be a contraindication to the use of NovoSeven.

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.

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 case of severe bleeds the product should be administered in hospitals preferably specialized in treatment of haemophilia patients with coagulation factor VIII or IX inhibitors, or if not possible in close collaboration with a physician specialized in haemophilia treatment.

The duration of the ambulatory treatment should not exceed 24 hours. 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.

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.

4.6 Pregnancy and lactation

From animal reproduction studies it was concluded that intravenous administration of NovoSeven had no effect upon foetal development, fertility or reproductive performance. It is not known whether NovoSeven can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. NovoSeven should only be given to pregnant women if clearly needed.

Use during lactation: It is not known whether NovoSeven is excreted in human milk. Caution should be exercised when NovoSeven is administered to lactating women.

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

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

Blood and lymphatic disorders	
Very rare (<1/10,000)	Few cases of coagulopathic disorders such as increased D-dimer and consumptive coagulopathy have been reported. Patients at increased risk of disseminated intravascular coagulation as described in 4.4 "Special warnings and precautions" should be carefully monitored.
Cardiac disorders	
Very rare (<1/10,000)	Myocardial infarction: Described below under 'serious thrombotic adverse reactions during the post-marketing period'.
Gastrointestinal disorders	
Very rare (<1/10,000)	Few cases of nausea have been reported.
General disorders and administration site conditions	
Rare (> 1/10,000, <1/1,000)	Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of NovoSeven is compliant with the recommended dosage as stated in 4.2 under "Dosage".
Very rare (<1/10,000)	Fever may occur. Pain, especially at injection site may also occur on rare occasions.
Investigations	
Very rare (<1/10,000)	Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin levels have been reported.
Nervous system disorders	
Very rare (<1/10,000)	Cerebrovascular disorders including cerebral infarction and cerebral ischaemia have been reported: Described below under 'serious thrombotic adverse reactions during the post-marketing period'.
Skin and subcutaneous tissue disorders	
Very rare (<1/10,000)	Skin rashes may occur.
Vascular disorders	
Very rare (<1/10,000)	Venous thrombotic events have been reported: Described below under 'serious thrombotic adverse reactions during the post-marketing period' Incidents of haemorrhage have been reported. NovoSeven is not expected to precipitate haemorrhage, but pre-existing haemorrhage may continue in case of insufficient efficacy or sub-optimal dosage regimen.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Serious adverse reactions reported during the post-marketing period include:

- Arterial thrombotic events such as myocardial infarctions or ischaemia, cerebrovascular disorders and bowel infarction. In the vast majority of cases the patients were predisposed to

arterial thrombotic disorders either due to underlying disease, age, atherosclerotic or current medical conditions as described in 4.4 “Special warnings and precautions”.

- Venous thrombotic events such as thrombophlebitis, deep vein thrombosis and hereto related pulmonary embolism. In the vast majority of cases the patients were predisposed to venous thrombotic events due to concurrent risk factors. Patients at increased risk of venous thrombotic disorders either due to concurrent conditions, previous history of thrombotic events, post surgery immobilisation or venous catheterisation should be carefully monitored.

Anaphylactic reactions have not been reported spontaneously during the post-marketing period, but patients with a history of allergic reactions should be carefully monitored.

There have been no reports of antibodies against factor VII in haemophilia A or B patients. Isolated cases of factor VII deficient patients developing antibodies against factor VII have been reported after treatment with NovoSeven. These patients have previously been treated with human plasma and/or plasma-derived factor VII. In two patients the antibodies showed inhibitory effect *in vitro*. Patients with factor VII deficiency treated with NovoSeven should be monitored for factor VII antibodies.

One case of angioneurotic oedema has been reported spontaneously in a patient with Glanzmann’s thrombasthenia after administration of NovoSeven.

4.9 Overdose

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

No other thrombotic complications from overdose have been reported, not even after treatment of a 6 year old boy with haemophilia A with inhibitors with 8-10 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coagulation factors, ATC code: B02B D08

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. 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 although clinical post marketing experience to date has not resulted in reporting of this as a significant adverse drug reaction.

5.2 Pharmacokinetic properties

Haemophilia A and B with inhibitors

Using a factor VII clot assay, the pharmacokinetic properties of NovoSeven were investigated in 25 non-bleeding and in 5 bleeding study episodes.

Factor VII clotting activities measured in plasma drawn prior to and during a 24-hour period after NovoSeven administration were analysed. Single dose pharmacokinetics of NovoSeven, 17.5, 35 and 70 µg per kg body weight exhibited linear behaviour. The median apparent volumes of distribution at steady state and at elimination were 106 and 122 ml/kg respectively in non-bleeding episodes and 103 and 121 ml/kg, respectively in bleeding episodes. Median clearance was 31.0 ml/h x kg and 32.6 ml/hx kg respectively in the two groups. The drug elimination was described by mean residence time and half-life. The figures were 3.44 h and 2.89 h (median values), respectively in non-bleeding episodes and 2.97 h and 2.30 h (median values), respectively in bleeding episodes.

The median *in vivo* plasma recovery was 45.6% in patients with non-bleeding episodes and 43.5% in patients with bleeding episodes.

Factor VII deficiency

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

Glanzmann's thrombasthenia

Pharmacokinetics of NovoSeven in patients with Glanzmann's thrombasthenia has not been investigated, but is 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Calcium chloride dihydrate
Glycylglycine
Polysorbate 80
Mannitol
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.

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

The NovoSeven package contains:
- 1 vial with white powder (NovoSeven) for solution for injection
- 1 vial 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.

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.

6.6 Special precautions for disposal

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.

- Take the syringe out of its package. Open the vial adapter pack. Keep the vial adapter in the pack while screwing it tightly onto the syringe. Take care not to touch the tip of the vial adapter.

- 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). Take care not to touch the spike of the vial adapter.

- Click the vial adapter onto the water vial. To inject the air into the vial, push 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 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(S)

EU/1/96/006/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT