Professional Information for NovoSeven®

Scheduling status S4

1. Name of the medicine

NovoSeven® 1 mg powder and solvent for solution for injection

NovoSeven® 2 mg powder and solvent for solution for injection

NovoSeven® 5 mg powder and solvent for solution for injection

2. Qualitative and quantitative composition

- NovoSeven® 1 mg (corresponds to 50 KIU) contains 1 mg per vial activated recombinant coagulation factor VIIa (eptacog alfa).
- NovoSeven® 2 mg (corresponds to 100 KIU) contains 2 mg per vial activated recombinant coagulation factor VIIa (eptacog alfa).
- NovoSeven® 5 mg (corresponds to 250 KIU) contains 5 mg per vial activated recombinant coagulation factor VIIa (eptacog alfa).

The activated recombinant coagulation factor VIIa (eptacog alfa) is produced in baby hamster kidney (BHK) cells by recombinant DNA technology.

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

1 KIU equals 1 000 IU (International Units).

Excipients with known effect

Contains sugar (10 mg sucrose per 1 ml vial).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection.

Freeze-dried powder: A white, homogenous lyophilisate.

Histidine solvent: A clear, colourless solution.

Reconstituted product: A clear, colourless solution.

The reconstituted solution has a pH of approximately 6,0.

4. Clinical particulars

4.1 Therapeutic indications

- NovoSeven® is intended for use in the treatment of patients with haemophilia with inhibitors to coagulation factor VIII and factor IX. The use of NovoSeven® is indicated for patients suffering life- or limb-threatening bleeds or requiring surgery and in home-treatment setting for early intervention to treat mild to moderate bleeding episodes.
- NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in patients with congenital FVII deficiency undergoing surgery or invasive procedures.
- NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those patients undergoing surgery or invasive procedures with Glanzmann's thrombasthenia with or without antibodies to GP IIb-IIIa and/or HLA, and with past or present refractoriness to platelet transfusions, or where platelets are not readily available.
- NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those patients with acquired haemophilia undergoing surgery or invasive procedures.

Severe postpartum haemorrhage

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

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a medical practitioner, experienced in the

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treatment of haemophilia and/or bleeding disorders.

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

Posology

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

Dose

NovoSeven® should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight.

Following the initial dose of NovoSeven® further injections may be repeated. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage, the invasive procedures or surgery being performed.

Paediatric population

Current clinical experience does not warrant a general differentiation in dosing between children below 18 years and adults, although young children (below 12 years) 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.

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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 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 (4,5 KIU) 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 treatment should not exceed 24 hours. If continued therapy is indicated the haemophilia treatment centre should be contacted.

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

Serious bleeding episodes:

The dosage varies according to the type and severity of the haemorrhages. As a guideline an initial dosage of 4,5 KIU (90 µg) per kg body weight is recommended. 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.

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A major bleeding episode may be treated for 2 – 3 weeks but can be extended beyond this if clinically warranted.

Surgery/invasive procedure:

An initial dose of 4,5 KIU (90 µg) per kg body weight should be given immediately before the procedure. The dose should be repeated after 2 hours and then 2 – 3 hours intervals for the first 24 – 48 hours depending on the surgery performed and the clinical status of the patient.

In major surgery, the dosage 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 two weeks of treatment. Patients undergoing surgery may be treated for up to 2 – 3 weeks until healing has occurred.

For patients with factor IX inhibitors or acquired antibodies to factor VIII, only experience of the use of NovoSeven® in minor surgery exists.

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

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adequate 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 range 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.

Severe postpartum haemorrhage

Dose, dose range and dose interval

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

Method of administration

For instructions on reconstitution of NovoSeven® before administration, see section 6.6.

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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

Known hypersensitivity to eptagoc alfa (the active ingredient), the excipients listed in section 6.1, or to mouse, hamster or bovine protein.

4.4 Special warnings and precautions for use

In patients receiving NovoSeven® after major surgery or in pathological conditions in which tissue factor may be expressed more extensively than considered normal e.g. conditions like advanced atherosclerotic disease, crush injury, liver failure, malignancy or septicaemia, there may be a risk of development of thrombotic events or induction of disseminated intravascular coagulation (DIC) in association with NovoSeven® treatment. Patients in such conditions receiving NovoSeven® should be kept under close observation for signs and symptoms of untoward activation of the coagulation system or thrombosis.

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 with liver disease, to patients undergoing major surgery, to post-operative patients, to pregnant or peripartum women, to neonates, or to patients at risk of thromboembolic events or DIC. In each of these situations, the potential benefit of treatment with NovoSeven® should be weighed against the risk of these complications.

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

As recombinant coagulation factor VIIa, NovoSeven® may contain trace amounts of mouse IgG, bovine IgG and other residual culture proteins (hamster and bovine serum proteins), the remote possibility exists that patients treated with NovoSeven® may develop hypersensitivity to these proteins. In such cases treatment with antihistamines IV 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 NovoSeven® immediately and contact their medical practitioner.

In case of severe bleeds NovoSeven® 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 medical practitioner specialised in haemophilia treatment.

In case of mild to moderate bleeding episodes, NovoSeven® may be administered at home; however this should only be done in close collaboration with a haemophilia centre where the patient is regularly followed up. The duration of home treatment should not exceed 24 hours.

If bleeding is not kept under control, hospital care is mandatory. Patients or carers should inform the medical practitioners or supervising hospital at the earliest possible opportunity about all usages of NovoSeven®.

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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).

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

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not receive NovoSeven®.

NovoSeven® contains less than 1 mmol sodium (23 mg) per injection, indicating that it is essentially "sodium free".

4.5 Interaction with other medicines 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. Anti-fibrinolytics are also used to reduce blood loss in women with postpartum

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haemorrhage. Experience with concomitant administration of anti-fibrinolytics and NovoSeven® treatment is however limited.

Based on a non-clinical study, it is not recommended to combine NovoSeven® and recombinant coagulation factor XIII (rFXIII). There are no clinical data available on interaction between rFVIIa and rFXIII.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

It is not known whether NovoSeven® can affect reproduction capacity.

Pregnancy

Safety in pregnancy has not been established.

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 NovoSeven® on pregnancy or on the health of the fetus/newborn 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/fetal development, parturition or postnatal development.

Breastfeeding

It is not known whether NovoSeven® is excreted in human breast milk. The excretion of NovoSeven® in milk has not been studied in animals. A decision on whether to continue/ discontinue breastfeeding or to continue/discontinue therapy with NovoSeven® should be made taking into account the benefit of breastfeeding to the child and benefit of NovoSeven® therapy to the woman.

Fertility

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Data from non-clinical studies as well as post-marketing data show no indication that NovoSeven® 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 a vehicle and use machines have been performed.

4.8 Undesirable effects

Clinical trials conducted in 484 patients (including 4 297 treatment episodes) with haemophilia A and B, acquired haemophilia, factor VII deficiency and Glanzmann's thrombasthenia have shown that adverse 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 reactions that can be assigned is rare (≥ 1/10 000, < 1/1 000).

The most frequent adverse reactions are pyrexia and rash (uncommon: > 1/1 000 to < 1/100), and the most serious adverse reaction are thromboembolic events.

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

System Organ Class	Side effects
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 decreased levels of AT • Coagulopathy
Immune system disorders	*Rare (≥ 1/10 000, < 1/1 000)* • Hypersensitivity **Frequency not known* • Anaphylactic reaction

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Gastrointestinal disorders	*Rare (≥ 1/10 000, < 1/1 000)* • Nausea
Nervous system disorders	*Rare (≥ 1/10 000, < 1/1 000)* • Headache
Vascular disorders	*Uncommon (≥ 1/1 000, < 1/100)* • Venous thromboembolic events: deep vein thrombosis, thrombosis at IV site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia *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) • Angina pectoris **Frequency not known* • Intracardiac thrombus
Skin and subcutaneous tissue disorders	*Uncommon (≥ 1/1 000, < 1/100)* • Rash (including allergic dermatitis and rash erythematous) • Pruritus and urticaria **Frequency not known* • Flushing • Angioedema

General disorders and administration site conditions	*Uncommon (≥ 1/1 000, < 1/100)* • Therapeutic response decreased. (It is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage, as stated in section 4.2.) • Pyrexia *Rare (≥ 1/10 000, < 1/1 000)* • Injection site reaction including injection site pain
Investigations	*Rare (≥ 1/10 000, < 1/1 000)* • Increased fibrin degradation products • Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin levels

**Adverse reactions reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known.*

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 factor VII deficiency.

In clinical trials of patients with factor VII deficiency, formation of antibodies against NovoSeven® and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). In some cases, the antibodies showed inhibitory effect *in vitro*. Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived factor VII, severe mutation of FVII gene, and overdose of NovoSeven®, were

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present. Patients with factor VII deficiency treated with NovoSeven® should be monitored for factor VII antibodies (see section 4.4).

Thromboembolic events – arterial and venous

When NovoSeven® is administered to patients outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (see side effects table above: Vascular disorders) (5,6 % in patients treated with NovoSeven® versus 3,0 % in placebo-treated patients) has been shown in a meta-analysis of pooled data from placebo-controlled trials conducted outside current approved indications in various clinical settings, each of these having distinct patient characteristics and hence different underlying risk profiles.

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

Thromboembolic events may lead to cardiac arrest.

Other special populations

Patients with acquired haemophilia

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

Women with severe postpartum haemorrhage

In an open-label randomised clinical trial, venous thromboembolic events were reported in 2 of 51 patients treated with a single dose of NovoSeven® (median dose 58 µg/kg) and none of 33 patients

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not treated with NovoSeven®; no arterial thromboembolic events were reported in either group.
In 4 non-interventional studies, venous thromboembolic events were reported in 3 of 358 (0,8 %) patients treated with NovoSeven® (median dose range 63 – 105 µg/kg) and arterial thromboembolic events were reported in 1 (0,3 %) patient treated with NovoSeven®.
For known contributing factors to thromboembolic risk associated with pregnancy and severe postpartum haemorrhage (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NovoSeven® is important. It allows continued monitoring of the benefit/risk balance of NovoSeven®. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

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 years) 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.
Treatment is symptomatic and supportive.

5. Pharmacological properties

Category and class: A 8.1 Coagulants, Haemostatics

Pharmacotherapeutic group: Blood coagulation factors, ATC code: B02BD08.

5.1 Pharmacodynamic properties

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.

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

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

Clinical efficacy and safety

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Congenital FVII deficiency

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

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

Severe postpartum haemorrhage

The efficacy and safety of NovoSeven® was assessed in 84 women with severe postpartum haemorrhage in a multicentre, open-label clinical trial. Patients were randomised either to treatment with a single dose of 60 µg/kg of NovoSeven® (in addition to standard of care; N = 42) or to reference therapy (standard of care alone; N = 42), following failure of uterotonics (sulprostone). The treatment groups were well balanced in terms of demographic characteristics and postpartum haemorrhage treatment prior to randomisation. Fibrinogen and tranexamic acid were part of standard of care.

Information on fibrinogen/tranexamic acid use was available from approximately 57 % of patients in the NovoSeven® group and 43 % of patients in the reference group. Of these, about 40 % of the patients in both groups received fibrinogen and/or tranexamic acid. Bleeding was considered to have stopped (i.e. treatment success) if the estimated blood flow decreased to less than 50 ml per 10 minutes within the 30 minutes following randomisation. If the bleeding was uncontrolled or intractable, invasive procedures were considered.

In the primary analysis, fewer women in the NovoSeven® group (21 vs 35) had at least one embolisation and/or ligation procedure compared to the reference group, corresponding to a statistically significant 40 % relative reduction in risk for the NovoSeven® group compared to the reference group (relative risk = 0,60 (95 % confidence interval: 0,43 – 0,84, p = 0,0012)).

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

Overview of main efficacy results for severe postpartum haemorrhage

	NovoSeven® (N = 42)	**Reference (N = 42)**	**Relative risk reduction (%) [95 % CI]**
Primary analysis			
Patients with invasive procedures – embolisation and/or ligation (%)	21 (50 %)	35 (83 %)	40 % [16 %; 57 %]*
Additional analysis			
Patients with invasive procedures – embolisation, ligation, uterine compression suture and/or hysterectomy **(%)**	21 (50 %)	38 (90 %)	45 % [24 %; 60 %]**
Patients with hysterectomy (%)	3 (7 %)	8 (19 %)	63 % [-32 %; 89 %]

Abbreviations: CI = confidence interval; N = number of patients

*p-value: p < 0,0012

**p-value: p < 0,0001

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 and/or placebo (3 doses each). The pharmacokinetic profiles indicated dose proportionality. The pharmacokinetics were similar across sex and ethnic groups.

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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 x kg, and 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. 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). Mean clearance was approximately 50 % higher in paediatric patients relative to adults (78 versus 53 ml/h x 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

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: 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

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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.

Severe postpartum haemorrhage

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

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.

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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:

24 months when the product is stored below 30 °C

36 months when the product is stored below 25 °C.

In vial:

After reconstitution, chemical and physical stability has been demonstrated for 6 hours at 25 °C and 24 hours at 2 °C – 8 °C.

From a microbiological point of view, NovoSeven® should be used immediately. If not used immediately, storage time and storage conditions prior to use are the responsibility of the user, and should not be longer than 24 hours at 2 °C – 8 °C unless reconstitution has taken place in controlled and validated aseptic conditions. The reconstituted solution should be stored in the vial.

In a 50 ml polypropylene syringe (for hospital use only):

Reconstitution must take place in controlled and validated aseptic conditions, by adequately trained health care providers.

Under these conditions, chemical and physical stability has been demonstrated for 24 hours at 25 °C when stored in a 50 ml polypropylene syringe. If not used immediately, the conditions prior to use are the responsibility of the user and the in-use storage time must not be longer than stated above.

6.4 Special precautions for storage

Store powder and solvent protected from light.

Do not remove powder and solvent vials or pre-filled syringe from the original outer carton to protect from light.

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Avoid freezing to prevent damage to the solvent vial or pre-filled syringe.

Do not freeze the reconstituted solution.

Safely dispose of any unused product as instructed by your health care provider.

Do not use after expiry date.

For storage conditions of the reconstituted solution, see section 6.3.

6.5 Nature and contents of container

NovoSeven® packages:

(a) NovoSeven® 1 mg (vial/syringe presentation):

- 1 x 2 ml clear, colourless, type I glass vial containing 1 mg (50 KIU) freeze-dried recombinant coagulation factor VIIa. The vial is closed with grey chlorobutyl rubber stopper, which is sealed with gold coloured aluminium cap covered with yellow red tamper-evident snap-off polypropylene cap.
- 1 x 3 ml clear, colourless, type I glass pre-filled syringe containing 1 ml Histidine solvent for reconstitution. The syringe consists of a glass barrel with a polypropylene backstop and bromobutyl rubber plunger. The syringe cap consists of bromobutyl rubber and polypropylene tamper evident seal. The plunger rod is made of polypropylene.

(b) NovoSeven® 2 mg (vial/syringe presentation):

- 1 x 2 ml clear, colourless, type I glass vial containing 2 mg (100 KIU) freeze-dried recombinant coagulation factor VIIa. The vial is closed with grey chlorobutyl rubber stopper which is sealed with a gold coloured aluminium cap covered with light blue tamper-evident snap-off polypropylene cap.
- 1 x 3 ml clear, colourless, type I glass pre-filled syringe containing 2 ml Histidine solvent for reconstitution. The syringe consists of a glass barrel with a polypropylene backstop and bromobutyl rubber plunger. The syringe cap consists of bromobutyl rubber and polypropylene tamper evident seal. The plunger rod is made of polypropylene.

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(c) NovoSeven® 5 mg (vial/syringe presentation):

- 1 x 12 ml clear colourless, type I glass vial containing 5 mg (250 KIU) freeze-dried recombinant coagulation factor VIIa. The vial is closed with grey chlorobutyl rubber stopper, which is sealed with a gold coloured aluminium cap covered with dark blue tamper-evident snap-off polypropylene cap.
- 1 x 10 ml clear, colourless, type I glass pre-filled syringe containing 5 ml Histidine solvent for reconstitution. The syringe consists of a glass barrel with a polypropylene backstop and bromobutyl rubber plunger. The syringe cap consists of bromobutyl rubber and polypropylene tamper evident seal. The plunger rod is made of polypropylene.

The NovoSeven® powder in vial/Histidine solvent in syringe product presentations come with a vial adaptor.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

NovoSeven® powder in vial/Histidine solvent in pre-filled syringe:

Reconstitution:

Always use aseptic technique

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

Signed: 

- 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 adaptor until resistance is felt. Hold the pre-filled syringe slightly tilted with the vial pointing downwards. Make sure not to aim the stream of solvent directly at the NovoSeven® powder as this will cause foaming. 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 adaptors.

If NovoSeven® is reconstituted and stored in a polypropylene syringe, it is recommended to use an in-line filter with a pore size of 25 micrometer upon administration.

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 solution, see section 6.3.

NovoSeven® is for intravenous bolus administration only. Favourable clinical results have been observed after administration of a dose of 3 – 6 KIU (60 – 120 µg) per kg body weight given at intervals of 2 hours or more according to the type of bleeding and the effect obtained in the treatment of life- and limb-threatening bleeds and in connection with surgery.

Administration:

Signed: _____

- 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 adaptor 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 product or waste material should be disposed of as instructed by your health care provider.

7. Holder of certificate of registration

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg

2196

8. Registration numbers

a) NovoSeven® 1 mg: Freeze-dried powder and 1 ml Histidine solvent pre-filled syringe: 44/8.1/0550

b) NovoSeven® 2 mg: Freeze-dried powder and 2 ml Histidine solvent pre-filled syringe: 44/8.1/0551

Signed: _____

c) NovoSeven® 5 mg: Freeze-dried powder and 5 ml Histidine solvent pre-filled syringe:

44/8.1/0552

9. Date of first authorisation

20 April 2012

10. Date of revision of the text

24 July 2023

Signed: _____