When bleeds happen, treat fast with NovoSeven®[1]

Suitable for people with haemophilia A or B with inhibitors[1]

NovoSeven® provides rapid bleed control

- 96.5% of CHwI# bleeds are resolved when treated with NovoSeven® within 1 hour of bleed onset*[2]
- Room temperature stable with 2–5 min infusion time for rapid access to treatment[1]

NovoSeven® has a favourable safety profile

- Low rate of thrombotic events[3]
- In clinical trials and over more than 20 years of post-marketing pharmacovigilance experience, no reported TMAs† and no confirmed neutralising antibodies[3,4]

NovoSeven® contains only rFVIIa and no other coagulation factors, such as FVIII or FIX[1]

NovoSeven®[1]	pd-aPCC[5^]
Qualitative composition • Recombinant factor VII activated	Qualitative composition • Factors II, IX and X mainly in non-activated form as well as activated Factor VII • Factor VIII coagulant antigen (FVIII C:Ag) is present at a concentration of up to 0.1 U/I U pd-aPCC) • Factors of the kallikrein-kinin system are present only in trace amounts, if at all

Bob, 62 years old, *enjoys fishing and boating with his wife. Bob lives with congenital haemophilia with inhibitors.*

* The SMART-7 study was a prospective, observational, single-arm, multi-centre, multi-national study investigating the safety and effectiveness of room-temperature stable NovoSeven® in people with haemophilia A or B with inhibitors in a real-world setting. The primary objective was to monitor reduced therapeutic response and neutralising antibodies to rFVIIa.

† Medically confirmed as possibly/probably related to NovoSeven®.

TMA – thrombotic microangiopathy

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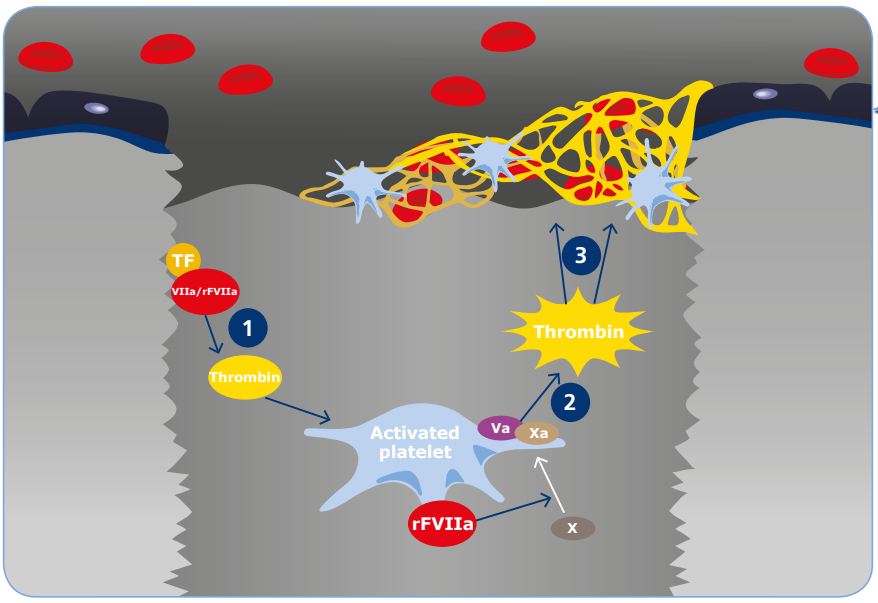
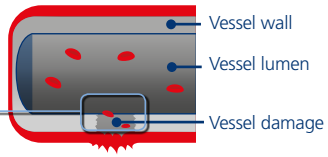
NovoSeven® Recombinant Factor VIIa

NovoSeven® (rFVIIa) works locally at the site of injury[6-9]





NovoSeven® works locally at the site of vascular injury, where tissue factor is exposed and activated platelets are found[6]

1. Binding of NovoSeven® to tissue factor initiates coagulation by generating small amounts of thrombin[7]
2. At pharmacological doses NovoSeven® directly activates factor X on the surface of activated platelets resulting in a "thrombin burst"[1,6-9]
3. The thrombin burst leads to the formation of a stable haemostatic plug which controls the bleeding[1,7]

Coagulation ability peaks rapidly (10 min) after dosing.[10]

Adapted from Hoffman M, et al., 2001.[6]

When bleeds happen, treat fast with NovoSeven®[1]

#CHwI – congenital haemophilia with inhibitors; ^pd-aPCC – plasma derived activated prothrombin complex concentrate; rFVII – recombinant factor VII; TF – tissue factor; TMA – thrombotic microangiopathy

NovoSeven® (rFVIIa) is the only bypassing agent recommended for the first line treatment of emergency bleeds for patients on emicizumab prophylaxis by EMA and FDA[11]

- No cases of thrombotic microangiopathy (TMA) or thromboembolism (TE) were observed with use NovoSeven® alone in patients receiving emicizumab prophylaxis (n=34). The median cumulative dose of NovoSeven® used was 700.8 µg/kg (range: 89 µg/kg to 15,654 µg/kg) per treatment episode.*, 11-13

*HAVEN1 was an open-label, randomised, crossover, clinical equivalency study.

References

1. NovoSeven® Packing insert. **2.** Benson G, et al., Poster presented at: ASH Congress; 3-6 December 2016; San Diego, California, United States. **3.** Neufeld EJ, et al. Blood Rev 2015; 29(S1):S34–S41. **4.** Data on File. Novo Nordisk. **5.** FEIBA® Summary of Product Characteristics. **6.** Hoffman M, Monroe DM. Thromb Haemost 2001; 85(6): 958–965. **7.** Jurlander B, et al. Semin Thromb Hemost 2001; 27(4): 373–384. **8.** Monroe DM, et al. Br J Haematol 1997; 99: 542–547. **9.** Monroe DM, et al. Blood Coagul Fibrinolysis 1998; 9(Suppl 1): S15–S20. **10.** Fernandez-Bello I, et al. Presented at: ISTH Annual Meeting; 23-26 June 2014; Milwaukee, Wisconsin, United States. **11.** National Hemophilia Foundation. MASAC Update. December 06, 2018. **12.** HEMLIBRA® Summary of Product Characteristics.**13.** Oldenburg J, Mahlangu JN, Kim B et al. N Engl J Med 2017;377(9):809-818.

NovoSeven®: Prescribing Information

NovoSeven® 1 mg (50 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection

Composition: eptacog alfa (activated), eptacog alfa (activated) is recombinant coagulation factor VIIa (rFVIIa) produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology, 1 mg/vial (corresponds to 50 KIU/vial). 1mg/ml eptacog alfa (activated) after reconstitution.

List of excipients:

Powder: Sodium chloride, Calcium chloride dihydrate, Glycylglycine, Polysorbate 80, Mannitol, Sucrose, Methionine, Hydrochloric acid, Sodium hydroxide

Solvent: Histidine, Hydrochloric acid, Sodium hydroxide, Water for injections

Indications: treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX >5 BU;
- patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration;
- patients with acquired haemophilia;
- patients with congenital FVII deficiency;
- patients with Glanzmann's thrombasthenia with antibodies to GP IIb-IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

Posology:

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

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 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:

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:

The recommended dose range 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. Limited clinical experience in long term prophylaxis in paediatric population has been gathered in the paediatric population below 12 years of age, with a severe clinical phenotype. Dose and frequency of injections for prophylaxis should be based on clinical response and adapted to each individual

Glanzmann's thrombasthenia:

The recommended dose 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.

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

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 it is not recommended to combine rFVIIa and rFXIII. There are no clinical data available on interaction between rFVIIa and rFXIII.

Undesirable effects:

Rare (> 1/10,000, < 1/1,000): Disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased level of AT, coagulopathy, hypersensitivity, headache, 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, nausea, injection site reaction including injection site pain, increased fibrin degradation products, increase in alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin.

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), rash (including allergic dermatitis and rash erythematous), pruritus and urticaria, therapeutic response decreased, pyrexia.

Inhibitory antibody formation: In post-marketing experience, there have been no reports of inhibitory antibodies against NovoSeven® or FVII in patients with congenital 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.

Not known: Intracardiac thrombus, anaphylactic reaction, flushing, angioedema.

Overdose: 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.

Adminstration: NovoSeven® (eptacog alfa activated) is administered intravenously over 2–5 minutes.

Caution: Some needleless connectors with an internal spike used with central venous access devices (CVADs) may be incompatible with the pre-filled glass syringe and prevent administration. Therefore, use of an alternative sterile 10ml luer-lock plastic syringe may be required for withdrawal and injection of the reconstituted solution. Follow the instructions for use for the CVAD and needleless connector.

Storage: 3 years shelf life when product is stored below 25°C. Store powder and solvent below 25°C and protect from light. Do not freeze solvent vial/ pre-filled syringe. After reconstitution, chemical and physical stability has been demonstrated for 6 hours at 25°C and 24 hours at 5°C.

It is recommended the product be used immediately after reconstitution.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.

Further information is available from:
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NovoSeven® Recombinant Factor VIIa

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