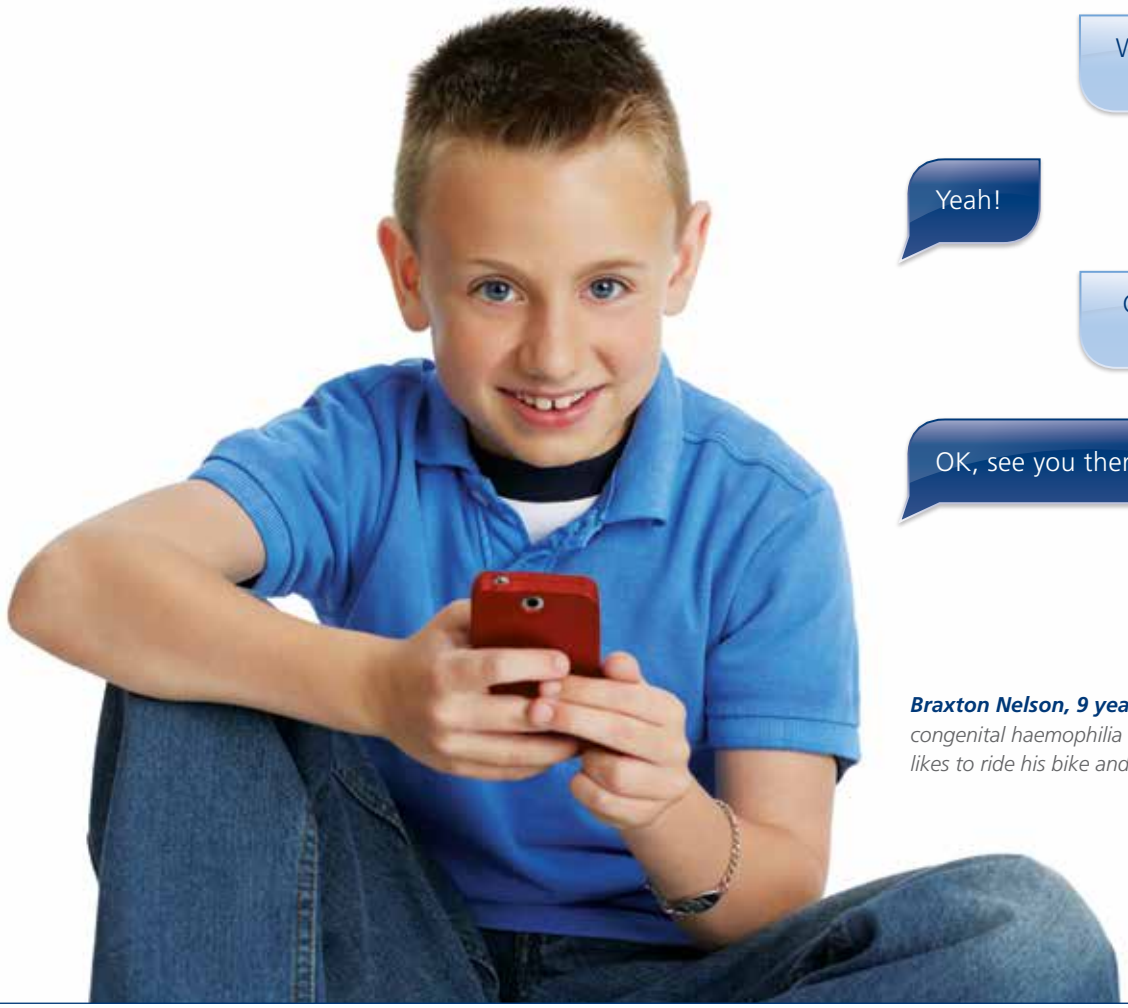
For people with congenital haemophilia with inhibitors...

NovoSeven® responds with speed to control their bleeds[1–4]



Braxton Nelson, 9 years old, *has congenital haemophilia with inhibitors and likes to ride his bike and play the drums.*

Please see Prescribing Information on page 18 of this brochure.

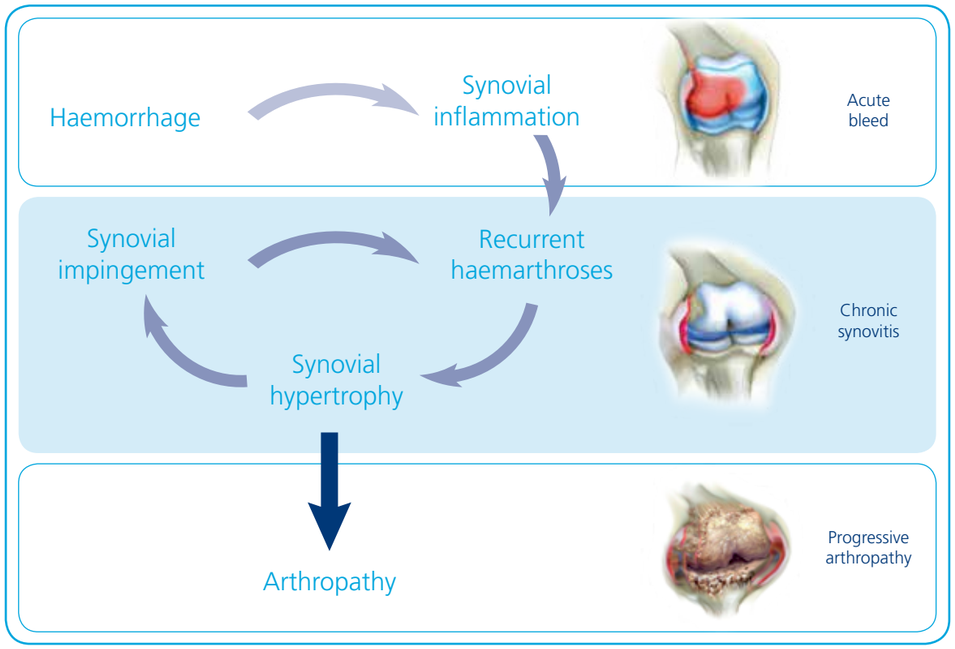
novo nordisk®

NovoSeven®
Recombinant Factor VIIa

Responding to the specific treatment needs of people with haemophilia with inhibitors

People with haemophilia with inhibitors present a special challenge

- Bleeds can be difficult to manage, resulting in potentially life-threatening bleeding[5–7]
- Joint bleeds can cause significant pain and difficulties with mobility and daily activities[8–10]
- Acute and recurrent joint bleeding can lead to greater joint damage[8,9]
- Poorer outcome following joint bleeds[10]



Adapted from Luck *et al.* 2004

The consequences of delayed treatment

- More blood in the joint[11]
- Longer time to bleeding resolution[12,13]
- A larger number of doses required to stop the bleeding[12]
- Chronic haemophilic synovitis, the result of recurrent haemarthrosis, leads to progressive arthropathy[8,9]
- Increased costs[12]

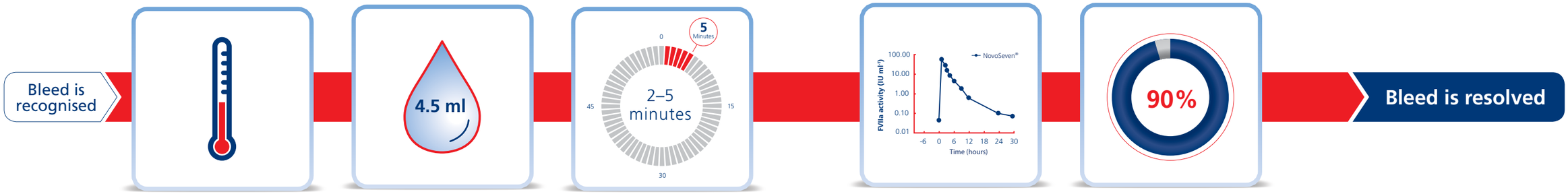
Appropriate patient management necessitates rapid bleed control

- World Federation of Hemophilia guidelines based on expert opinion recommend that treatment should ideally start **within 2 hours** of the onset of bleeding[14]
- Furthermore, a bypassing agent with a favourable safety profile that can be used effectively and conveniently throughout a person's lifetime is a desirable option[7,15,16]
- Home treatment may enable early intervention[17]

For people with congenital haemophilia with inhibitors…

NovoSeven® is fast from start to finish[1,2,4]

NovoSeven® (90 µg/kg)



Rapid access to treatment
Room temperature stable for up to 3 years at <25°C[4]

Rapid reconstitution
Low volume makes NovoSeven® fast to reconstitute and administer*[4]

Rapid administration
2–5 minutes to infuse[4]

Rapid activity
Achieves maximum activity in 5–10 minutes[1]

Rapid bleed control
90% of joint bleeds controlled within 9 hours[3,17,18]

NovoSeven® resolves the bleed rapidly with established efficacy[1,3,17,18]

*Example of volume for a 50-kg person.

Please see Prescribing Information on page 18 of this brochure.

Dad, can I ride my bike to the park?

OK, don't forget your helmet.

I won't.

Be safe!

Braxton Nelson, 9 years old, *has congenital haemophilia with inhibitors and likes to ride his bike and play the drums.*

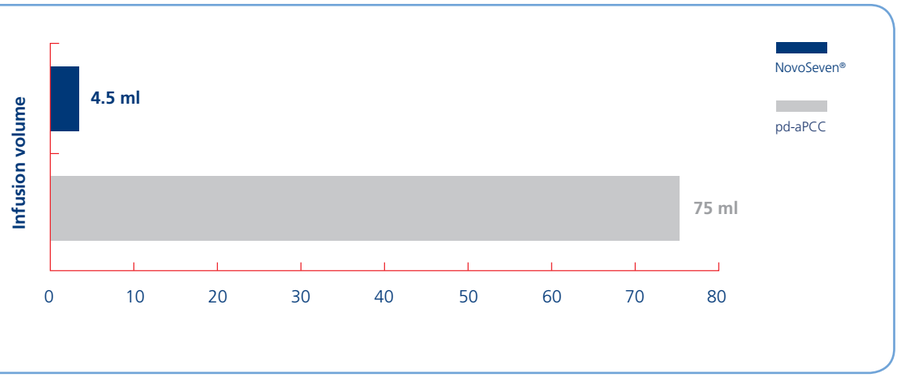
NovoSeven®
Recombinant Factor VIIa

For people with congenital haemophilia with inhibitors…

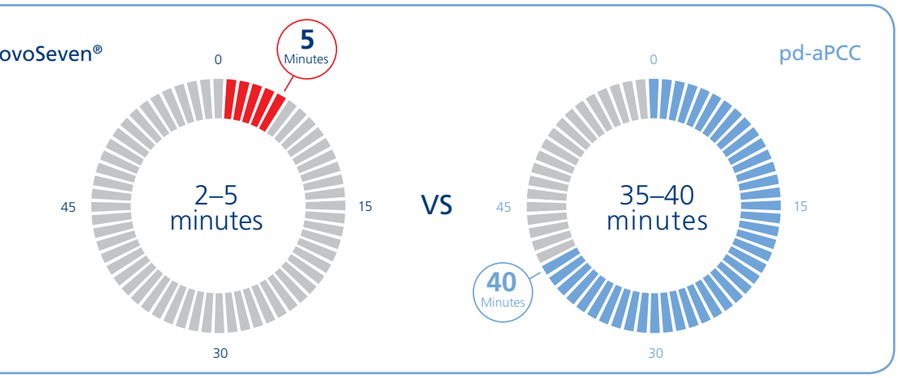
Fast and easy treatment access and administration facilitate rapid bleed control[1,3]

Low infusion volume and rapid administration make treatment faster

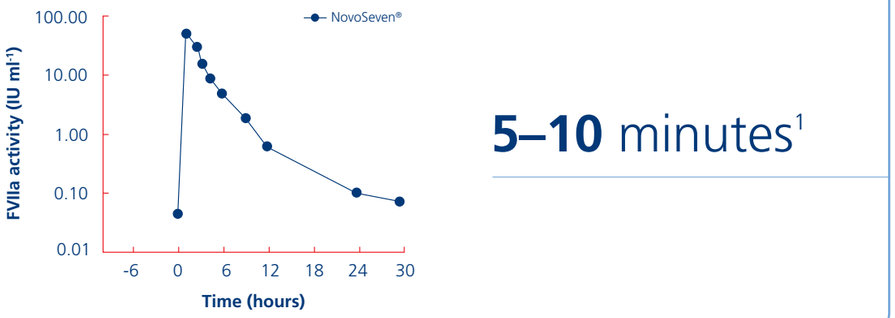
- Room temperature stability (up to 3 years at <25°C)[4]
- Low infusion volume (4.5 ml) for fast reconstitution and administration versus 75 ml for pd-aPCC*[4,19]



- **Rapid administration:** only 2–5 minutes versus 35–40 minutes for pd-aPCC[4,19]



- **Rapid activity:** achieves maximum activity in 5–10 minutes[1]

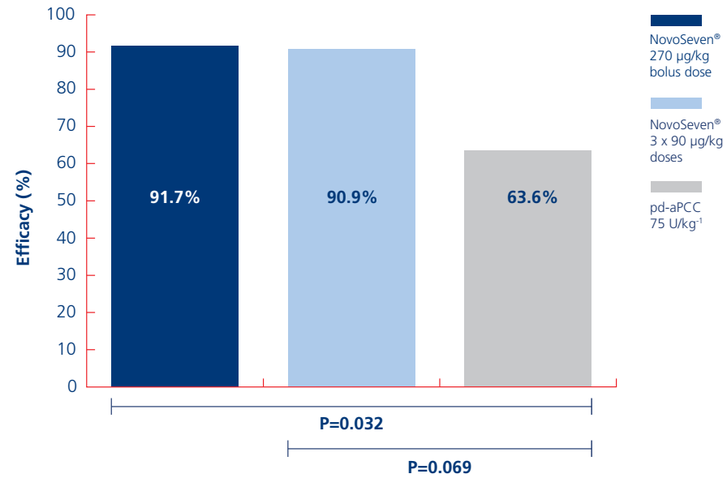


5–10 minutes[1]

*Example of volume for a 50-kg person.

90% of joint bleeds controlled within 9 hours versus 63% with pd-aPCC[3]

- Efficacy defined as the percentage of patients not requiring rescue medication within 9 hours of initiation of treatment



Adapted from Young *et al.* 2008

I'm bringing my new bike!

Cool, do you like it?

Yeah, it's blue and really fast!

Braxton Nelson, 9 years old, *has congenital haemophilia with inhibitors and likes to ride his bike and play the drums.*

NovoSeven®
Recombinant Factor VIIa

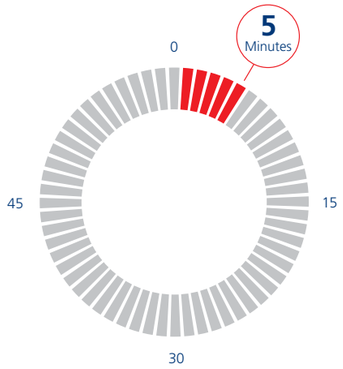
Please see Prescribing Information on page 18 of this brochure.

For people with congenital haemophilia with inhibitors…

Fast and easy treatment access and administration facilitate rapid bleed control[1,3]

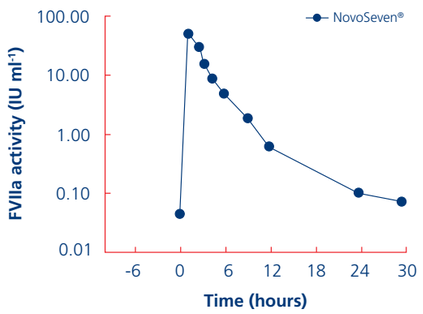
Low infusion volume and rapid infusion make treatment faster

- Room temperature stability (up to 3 years at <25°C)[4]
- Low infusion volume (4.5 ml) for fast reconstitution and administration*[4]
- **Rapid administration:** only 2–5 minutes[4]



2–5 minutes[4]

- **Rapid activity:** achieves maximum activity in 5–10 minutes[1]

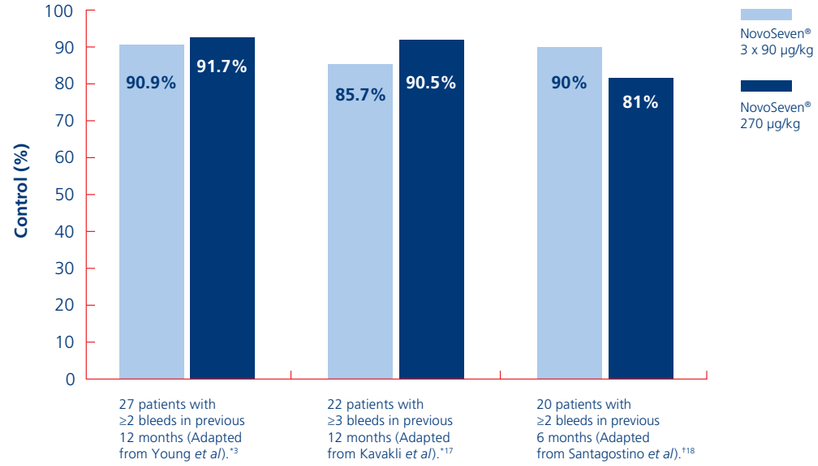


5–10 minutes[1]

*Example of volume for a 50-kg person.

NovoSeven® has established proven efficacy[3,17,18]

- 90% of joint bleeds controlled within 9 hours[3,17,18]



*Bleeding control defined as percentage of patients not requiring rescue medication.
†Bleeding control defined as rates of success and partial response as per visual analogue scale and clinical assessment.

I'm bringing my new bike!

Cool, do you like it?

Yeah, it's blue and really fast!

Braxton Nelson, 9 years old, *has congenital haemophilia with inhibitors and likes to ride his bike and play the drums.*

NovoSeven®
Recombinant Factor VIIa

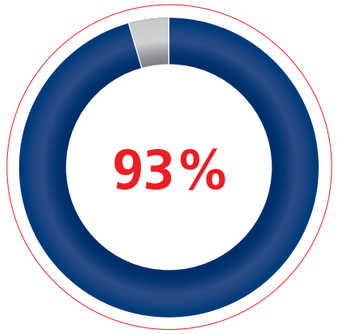
Please see Prescribing Information on page 18 of this brochure.

For people with congenital haemophilia with inhibitors...

NovoSeven® resolves the bleed rapidly with established efficacy[1,3,17,18]

Effective bleed control

- 93% of bleeds controlled with 1–3 doses*[2]



Percentage of bleeds controlled with **1–3 doses***[2]

- Equal efficacy of 270 µg/kg and 3 x 90 µg/kg doses in achieving haemostasis with a favourable safety profile[3]

Effective haemostatic coverage independent of bleed type and severity

- Comparable efficacy in muscle, joint and target joint and mucocutaneous bleeding episodes[2,20]
- Successful bleed resolution with NovoSeven® reduces pain[21]

*Efficacy defined as no use of additional haemostatic medication within 12 hours of the last dose for treatment of a bleed.

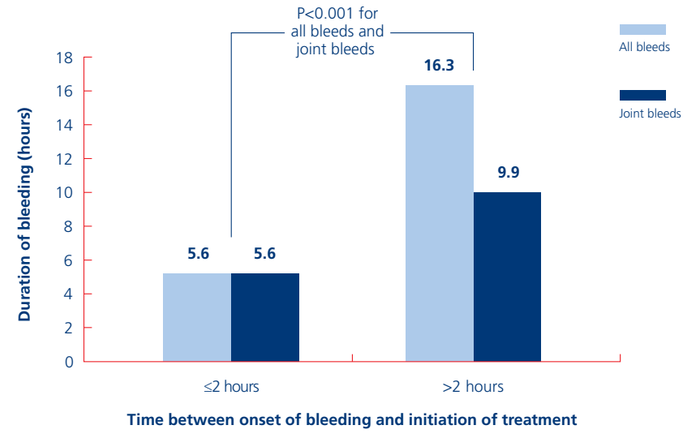
Please see Prescribing Information on page 18 of this brochure.

World Federation of Hemophilia guidelines based on expert opinion recommend that treatment should ideally start within 2 hours of the onset of bleeding[14]

Early treatment with NovoSeven® reduces the duration of bleeding episodes[21]

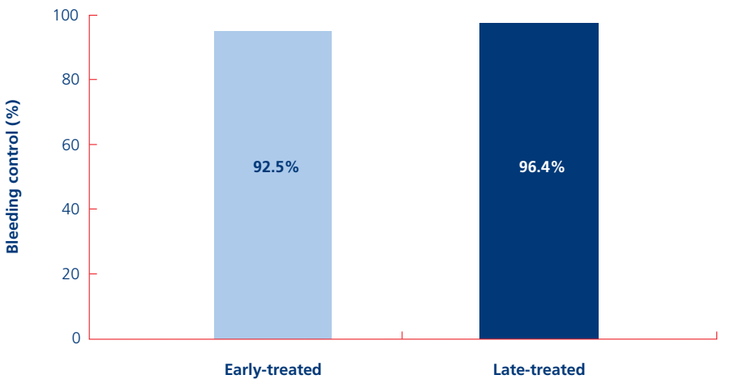
- Significantly shorter duration of bleeding if treatment with NovoSeven® started within 2 hours (P<0.001)[21]

Duration of bleeding episodes by time to treatment initiation[21]



NovoSeven® provides effective bleed control even if unable to treat early[2]

Early-treated (≤2 h) and late-treated (>2 h) bleeds responded equally well[2]



NovoSeven®
Recombinant Factor VIIa

For people with congenital haemophilia with inhibitors...

NovoSeven® provides the confidence of recombinant safety

The first and only recombinant bypassing agent

- Manufactured using recombinant technology, which does not employ human plasma or blood products[4,15]

Established safety profile

- No inhibitory antibodies reported in post-marketing experience*[4]
- No treatment-related anaphylactic reactions[4]
- Minimal risk of thrombotic events[4,22]

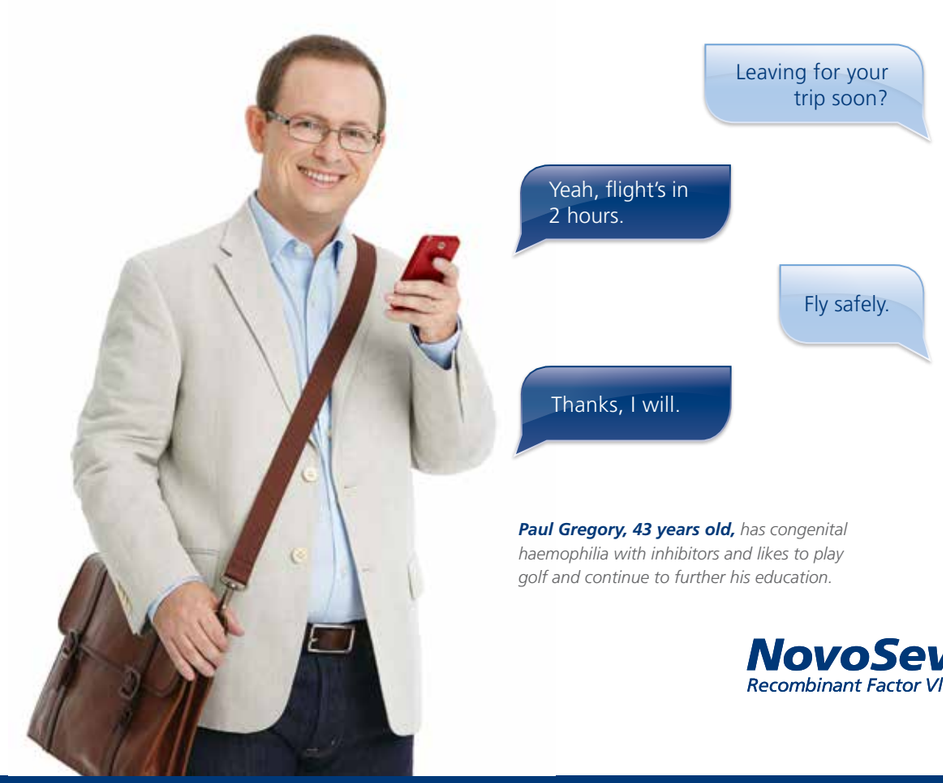
Does not induce anamnesis

- Pure FVIIa does not contain FVIII, FIX or respective antigens[15]
- pd-aPCC (plasma-derived) contains low levels of FVIII antigen and FIX[19]
- World Federation of Hemophilia guidelines recommend the avoidance of FVIII-containing products for patients undergoing immune tolerance induction therapy[14]

May be combined with anti-fibrinolytics[4]

*In people with congenital haemophilia with inhibitors.

Please see Prescribing Information on page 18 of this brochure.



Paul Gregory, 43 years old, *has congenital haemophilia with inhibitors and likes to play golf and continue to further his education.*

NovoSeven®
Recombinant Factor VIIa

For people with congenital haemophilia with inhibitors...

NovoSeven® provides the confidence of recombinant safety

The first and only recombinant bypassing agent

- Manufactured using recombinant technology, which does not employ human plasma or blood products[4,15]

Established safety profile

- No inhibitory antibodies reported in post-marketing experience*[4]
- No treatment-related anaphylactic reactions[4]
- Minimal risk of thrombotic events[4,22]

Does not induce anamnesis

- Pure FVIIa does not contain FVIII, FIX or respective antigens[15]
- World Federation of Hemophilia guidelines recommend the avoidance of FVIII-containing products for patients undergoing immune tolerance induction therapy[14]

May be combined with anti-fibrinolytics[4]

*In people with congenital haemophilia with inhibitors.

Please see Prescribing Information on page 18 of this brochure.

Paul Gregory, 43 years old, *has congenital haemophilia with inhibitors and likes to play golf and continue to further his education.*

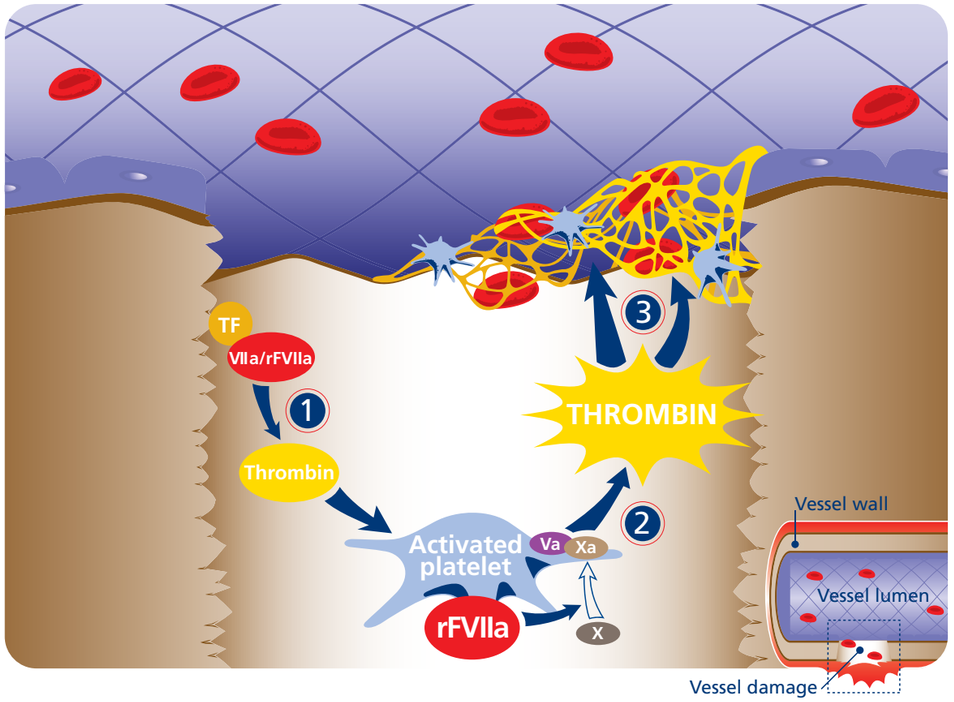
NovoSeven®
Recombinant Factor VIIa

For people with congenital haemophilia with inhibitors...

NovoSeven® responds with a unique, targeted mode of action[4,23–28]

Works locally at the site of vascular injury

- Binds directly to activated platelets to initiate the coagulation process, which results in the formation of a stable haemostatic plug at the site of the bleed[4,28]



Binds

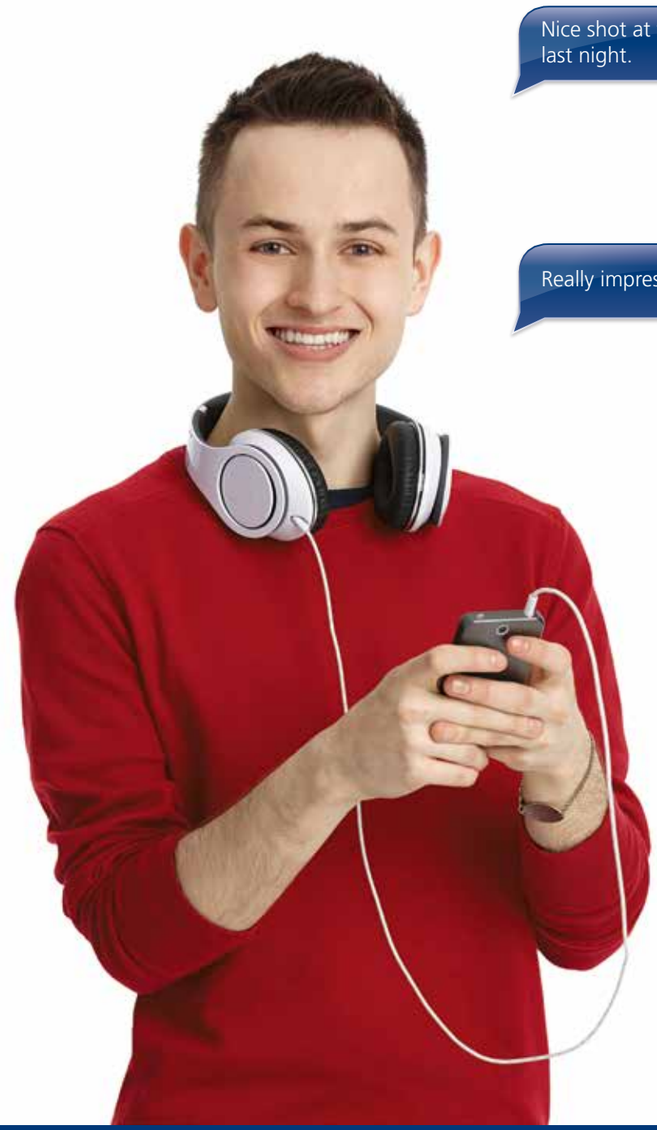
1 Binding of rFVIIa to tissue factor initiates coagulation, generating small amounts of thrombin[4,28]

Activates

2 At pharmacological doses, rFVIIa directly activates FX on the surface of activated platelets, resulting in a thrombin burst[4,28]

Controls

3 The thrombin burst leads to the formation of a stable haemostatic plug, which controls the bleeding[28,29]



Louis Marlow, 21 years old, *has congenital haemophilia with inhibitors and likes to go to music festivals and travel with his friends.*

Please see Prescribing Information on page 18 of this brochure.

NovoSeven® Recombinant Factor VIIa

For people with congenital haemophilia with inhibitors...

NovoSeven® with pre-filled syringe responds with rapid bleed control[1,4]

Fewer steps, for fast and convenient reconstitution[4]

- Eliminates the necessity to draw the solvent up into the syringe separately[4]
- Enables a simple reconstitution process due to fewer handling steps[4]

Ready for immediate use with room-temperature stable formulation

- User-friendly formulation provides the convenience of storing and transporting without refrigeration[1]
  - — Room temperature stability (up to 3 years at <25°C)[4]

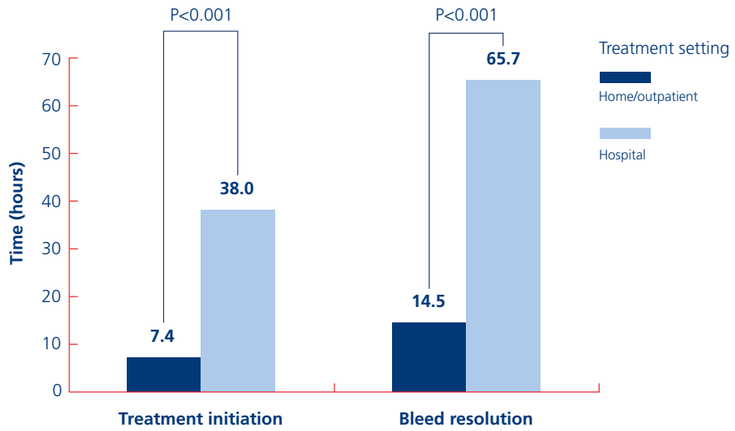
Flexible dosing

- No maximum daily dose restrictions[4]
- Short dosing interval — as quickly as every 2 hours[4]
- Consistent ≈90% efficacy and proven safety profile with either 3 x 90 µg/kg or 270 µg/kg[2,3,17,18]
- Broad range of vial sizes facilitates accurate dosing (1 mg, 2 mg, 5 mg and 8 mg)[4]

Suitable for home-based treatment[12,13,30] (for applicable markets)

- Home-based treatment facilitates early intervention, which is associated with increased efficacy and can also reduce costs related to bleeding

Effect of treatment setting on time to treatment initiation and bleed resolution[12]



Adapted from Kavakli *et al*. 2010

NovoSeven® travel case (for applicable markets)

- Light and easily portable pack ensures NovoSeven® is on hand for patients to use wherever they go

NovoSeven® Recombinant Factor VIIa

Novo Nordisk® is committed to providing you support and services

[Please insert local services here.]

Prescribing Information

NovoSeven® 1 mg (50 KIU) powder and solvent for solution for injection
NovoSeven® 2 mg (100 KIU) powder and solvent for solution for injection
NovoSeven® 5 mg (250 KIU) powder and solvent for solution for injection
NovoSeven® 8 mg (400 KIU) powder and solvent for solution for injection

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, 2 mg/vial, 5 mg/vial, 8mg/vial (corresponds to 50 KIU/vial, 100 KIU/vial, 250 KIU/vial, 400 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
  and/or HLA, and with
  transfusions.

Posology:

Haemophilia A or B w
anamnestic response:

Mild to moderate bleedinc

Early intervention has beer
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.

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: 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,
emia, peripheral arterial
pectoris, nausea, injection
creased fibrin degradation
se, alkaline phosphatase,

omboembolic events (deep
e, pulmonary embolism,
ortal vein thrombosis, renal
ial 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 with inhibitors. 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: Three cases of overdose have been reported in patients with haemophilia in 13 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.

Storage: 3 years shelf life when product is stored below 25°C. 2 years shelf life when product is stored below 30°C. Store powder and solvent vial / pre-filled syringe below 30°C. Store powder and solvent vial / pre-filled syringe protected from light. Do not freeze. It is recommended the product be used immediately after reconstitution.

Way of delivery: Medical prescription.

Authorisation holder: Novo Nordisk A/S, Bagsvaerd, Denmark.

Date of last revision: April 2013.

For more detailed information please consult the EMEA product information.

Novo Nordisk® is a registered trademark owned by Novo Nordisk A/S. NovoSeven® is a registered trademark owned by Novo Nordisk Health Care AG, Thurgauerstrasse 36-38, 80 Zürich, Switzerland, Tel +41432224300.

Please update with local product information.

Broad range of vial sizes[4]

References

1. Bysted BV *et al.,* Haemophilia 2007; 13: 527 – 532. **2.** Windyga J *et al.,* Efficacy and safety of rFVIIa, used as comparator in development of a new rFVIIa analogue: data from a phase 3 trial on vatreptacog alfa in haemophilia patients with inhibitors. Poster presented at: WFH 13th International Musculoskeletal Congress 2013; 2013 April 18–21, Chicago, IL, USA. **3.** Young G *et al.,* Haemophilia 2008; 14(2): 287 – 294. **4.** NovoSeven® Summary of Product Characteristics. **5.** Bolton-Maggs PHB, Pasi KJ. Lancet 2003; 361: 1801 – 1809. **6.** Colvin BT *et al.,* Haemophilia 2008; 14: 361 – 374. **7.** DiMichele DM. Haemophilia 2000; 6(suppl 1): 38 – 40. **8.** Lafeber FPJG *et al.,* Haemophilia 2008; 14(suppl 4): 3 – 9. **9.** Luck JL *et al.,* J Am Acad Orthop Surg 2004; 12: 234 – 245. **10.** Morfini M *et al.,* Haemophilia 2007; 13: 606 – 612. **11.** Rodriguez-Merchan EC *et al.,* Haemophilia 2011; 17 (suppl 2): 1 – 23. **12.** Kavakli K *et al.,* Haemophilia 2010; 16: 487 – 494. **13.** Salaj P *et al.,* Haemophilia 2009; 15: 752 – 759. **14**. Srivastava A *et al.,* Haemophilia 2012: 1 – 47. **15.** Croom KF, McCormack PL. Biodrugs 2008; 22(2): 121 – 136. **16.** De Paula EV *et al.,* J Thromb Haemost 2012; 10: 81 – 89. **17.** Kavakli K *et al.,* Thromb Haemost 2006; 95: 600 – 605. **18.** Santagostino E *et al.,* Thromb Haemost 2006; 4: 367 – 371. **19.** FEIBA Summary of Product Characteristics, 2007. **20.** Key NS *et al.,* Thromb Haemost 1998; 80: 912 – 918. **21.** Salaj P *et al.,* Haemophilia 2012: 1 – 3. **22.** Abshire T. Semin Hematol 2008; 45(suppl 1): S3 – S6. **23.** Monroe DM *et al.,* Br J Haematol 1997; 99: 542 – 547. **24.** Monroe DM *et al.,* Blood Coagul Fibrinolysis 1998; 9(suppl 1): S15 – S20. **25.** Monroe DM, Hoffman M. Arterioscler Thromb Vasc Biol 2006; 26: 41 – 48. **26.** Diness V *et al.,* Thromb Res 1992; 67(2): 233 – 241. **27.** Jurlander B *et al.,* Semin Thromb Hemost 2001; 27(4): 373 – 383. **28.** Hedner U, Lee CA. Haemophilia 2011; 17: e172 – e182. **29.** Hoffman M, Dargaud Y. J Thromb Haemost 2012; 10: 1478 – 1485. **30.** Odeyemi IAO, Guest JF. J Med Econ 2002; 5: 1 – 15.

NovoSeven®
Recombinant Factor VIIa

NovoSeven®, the first and only recombinant bypassing agent, resolves bleeds rapidly and effectively[1–4]

Established efficacy

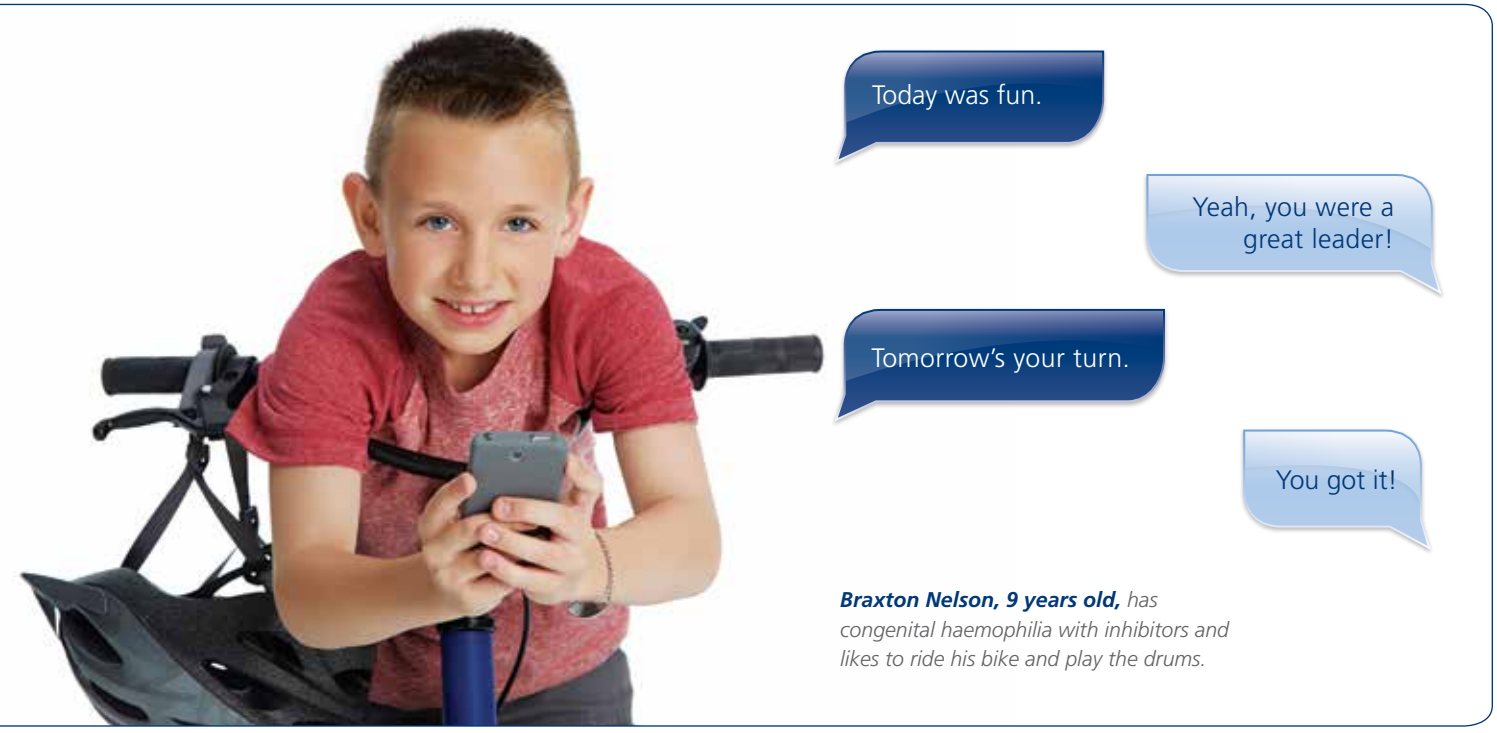
- **93%** of bleeds controlled with 1–3 doses[2]
- **90%** of joint bleeds controlled within 9 hours[3]
- Equal efficacy of 270 µg/kg and 3 x 90 µg/kg doses in achieving haemostasis[3]

Rapid initiation and administration

- Fewer steps, fast reconstitution with pre-filled syringe[4]
- Rapid infusion: only **2–5 minutes**[4]

Established safety profile

- Manufactured using **recombinant** technology, which does not employ human plasma or blood products[4,15]
- No inhibitory antibodies reported in post-marketing experience*[4]



Braxton Nelson, 9 years old, *has congenital haemophilia with inhibitors and likes to ride his bike and play the drums.*

*In people with congenital haemophilia with inhibitors.

Please see Prescribing Information on page 18 of this brochure.

novo nordisk®

NovoSeven®
Recombinant Factor VIIa