

NovoSeven[®]: a reliable partner in a changing landscape^{1,2}



Sid, 28 years old, works for a specialty pharmacy.
He enjoys travelling with his wife and likes to cook.
Sid lives with congenital haemophilia with inhibitors
and underwent knee replacement surgery.



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Emergency bleeds happen

12
per 1000
PATIENT-YEARS³

Congenital Haemophilia with Inhibitors (CHwI)

In the 1990s, the mortality for patients with congenital haemophilia A or B who develop inhibitors, regardless of severity, had dropped by half versus the 1970's ($P < 0.001$). The development of inhibitors was no longer associated with increased mortality in severe haemophilia, as the mortality rates in patients with inhibitors decreased to the level seen in patients without inhibitors.³

The longer a bleed remains untreated, the more cumulative damage done. CHwI patients know to treat as early as possible upon recognising a bleed.^{4,5}

Patients with CHwI will seek treatment primarily at Haemophilia Treatment Centres (HTCs) but will choose the nearest emergency room if they do not know/have access to a HTC, or in an emergency if:^{6,7}



They cannot access a vein



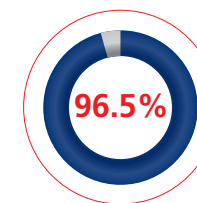
They have run out of medicine



They need emergency surgery (e.g. appendectomy) or have suffered an acute trauma (e.g. an accident)



Treat fast with NovoSeven®



Efficacy:

96.5% efficacy when treated within 1 hour of bleed onset^{††8}



Safety profile:

A pure rFVIIa that does not contain FVIII or FIX and works only at the site of vascular injury^{1,9-12}



Speed:

Low infusion volume results in rapid preparation and administration^{1,13}



Convenience:

Practical in-hospital storage and easy portability for out-patients^{†1}



Reliability:

30 years of research and clinical experience across more indications than any other agent^{1,2,14,15}



Jack, 7 years old, and his twin brother James enjoy video games and like to pretend they're boxing. Jack 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.⁸

† Post-hoc sub-analysis of SMART-7™ assessed haemostatic response to NovoSeven® in a real-world setting where time to first treatment was under 1 hour: a total of 318/618 bleeding episodes treated with rFVIIa monotherapy and with (1) valid efficacy assessment, (2) no missing time for bleed start, (3) no missing time for any dose administration, and (4) valid time to first treatment were included in the analysis. Effective = patient reported that the bleed "stopped"; Partially effective = patient reported that the bleed "slowed"; Ineffective = patient reported that the bleed "worsened/no change".⁸

‡ In a room temperature environment of 25°C.¹

Is your hospital ready for a changing landscape?

A new prophylaxis treatment for CHwI (emicizumab) has arrived:

- It has a much longer half-life than the bypassing agents (BPAs), allowing it to remain in the bloodstream at therapeutic levels for a longer period of time ($T_{1/2}=26.7$ days vs. $T_{1/2}=<1$ day)¹⁵
- Patients still use BPAs to treat bleeds while taking emicizumab (75 of 104 patients required the use of a BPA in the HAVEN1 study)^{5,16}



NovoSeven® (rFVIIa) is the only BPA recommended for the first line treatment of emergency bleeds or patients on emicizumab prophylaxis by EMA and FDA⁵

- No cases of thrombotic microangiopathy (TMA) or thromboembolism (TE) were observed with use of 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^{*5,15,16}

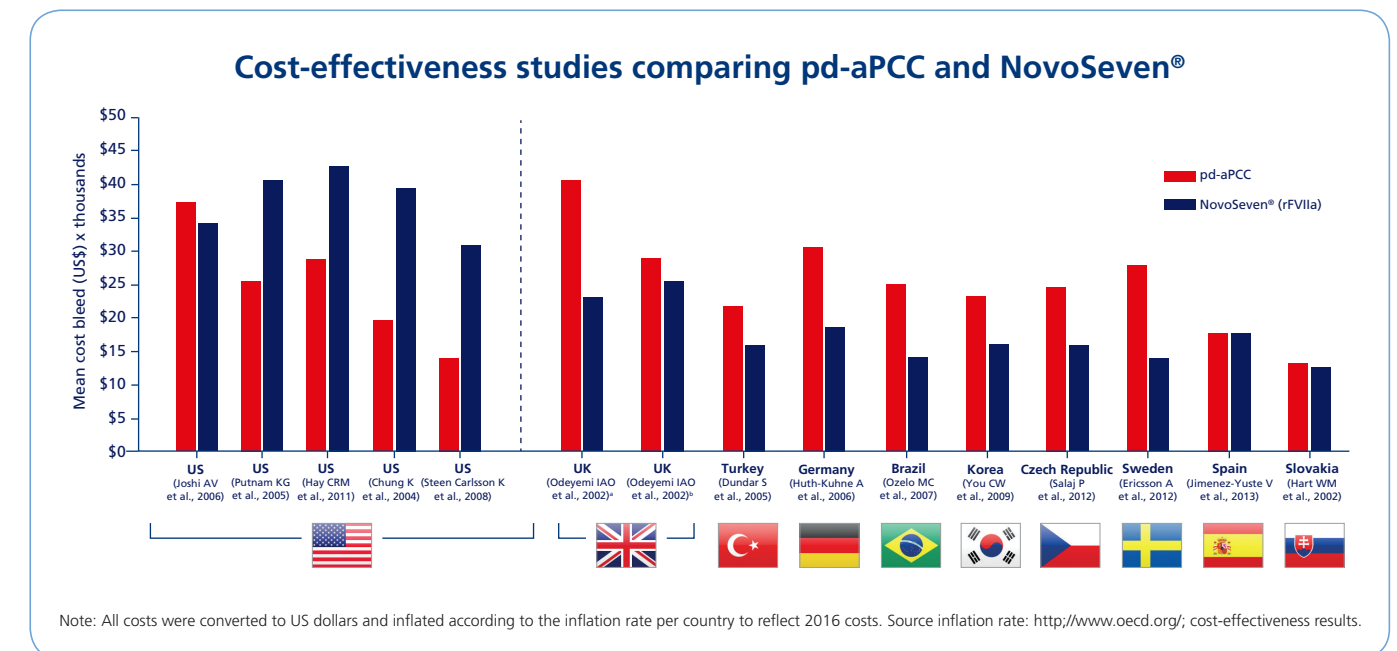
The right choice of **BPA** for the emergency treatment of bleeds is now critical



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

Can you afford not to consider cost-effectiveness?

NovoSeven® used first-line for emergency bleeds is cost-effective around the world¹⁷⁻³¹



- Regardless of the NovoSeven® starting dose used to treat acute bleeding episodes (90 µg/kg or 270 µg/kg), the total dose and drug costs are equivalent³²
- With no risk of anamnestic response, NovoSeven® can save hospitals up to 20% when used to manage acute bleeds prior to ITI therapy, compared with pd-aPCC²²
- Stability of NovoSeven® at room temperature may reduce product wastage and associated costs³³

Prepare yourself for emergencies: stock your hospital pharmacy and treat fast with NovoSeven®

When bleeds happen you need established **efficacy**...

Unsurpassed effective bleed resolution

96.5%

Of responses were rated as effective when treated with NovoSeven® **within one hour of bleed onset***†8

>4x

More patients achieved bleed resolution with a single dose of NovoSeven® 270 µg/kg vs. those treated with pd-aPCC 75 IU/kg (36.4% vs. 8.3%, P=0.032)‡34

Established dosing regimen for serious bleeds:

An initial dose of 90 µg/kg of body weight is recommended as early as possible, and could be administered on the way to the hospital¹



Over 30 years of research and clinical experience^{1,2}



...and **convenient safety profile**

NovoSeven® has a favourable and established safety profile with more than 5.4 million doses administered since 1996^{2,32,35-39}

NovoSeven® is the **only recombinant bypassing agent** containing only rFVIIa and no other coagulation factors, such as FIX or FIXa.^{1,40}

- **Does not induce an anamnestic response** prior to immune tolerance induction (ITI) therapy⁴¹
- Zero cases of thrombotic microangiopathy (TMA) when used in combination with emicizumab¹⁵

At pharmacological doses, NovoSeven® directly activates Factor X on the surface of activated platelets **only at the site of vascular injury**, it is **therefore associated with a low incidence of thromboembolic events** (TEs)^{1,9-12,15,19,42}

- Regardless of concomitant treatment with antifibrinolytics¹
- Regardless of concomitant treatment with emicizumab¹⁶

Bob, 63 years old, enjoys playing the guitar, fishing and boating with his wife. Bob lives with congenital haemophilia with inhibitors.



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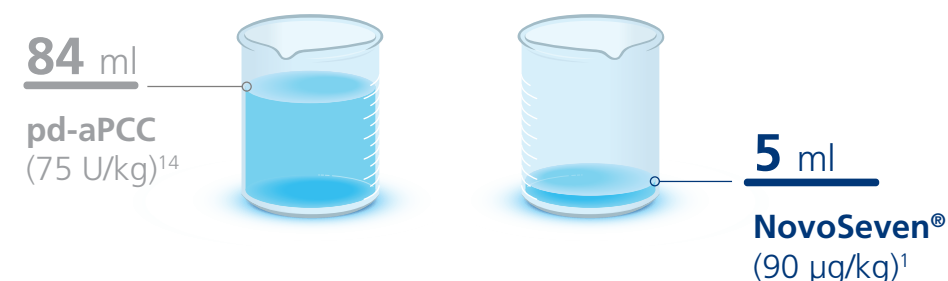
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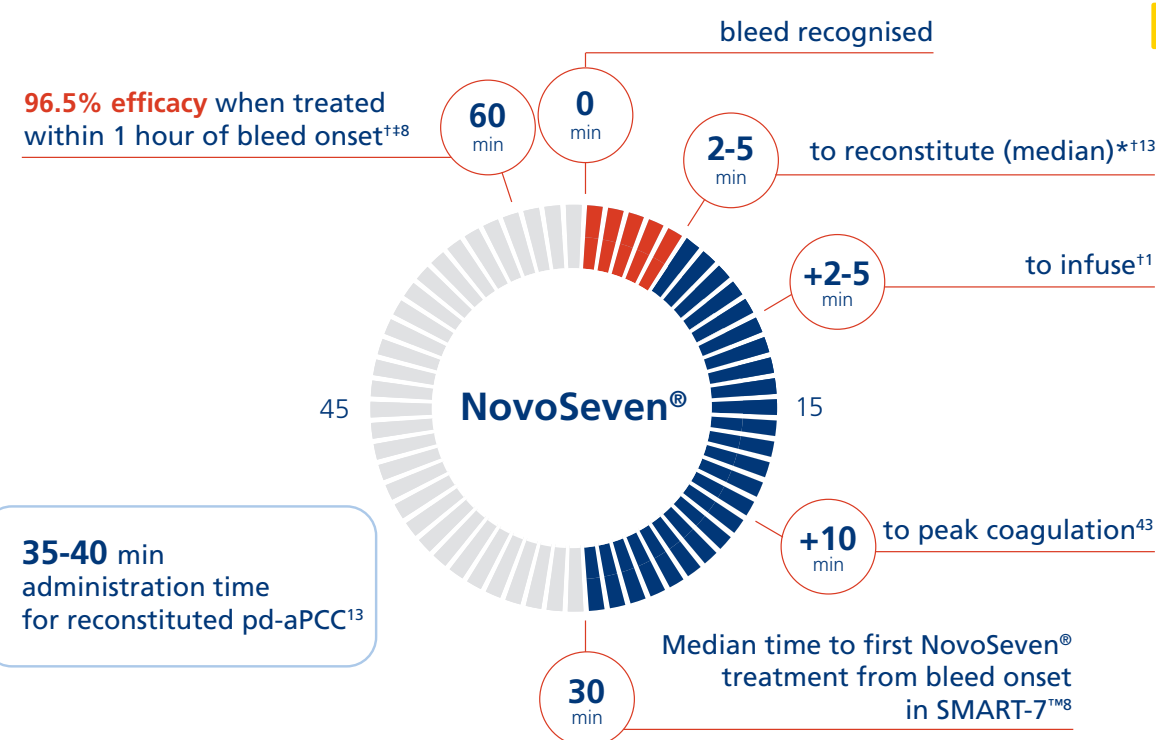
When treating bleeds time is of the essence^{4,6,7}

Low volume, rapid reconstitution and infusion

NovoSeven® has a lower infusion volume, which means **rapid reconstitution** and **rapid infusion** compared with pd-aPCC.¹³



30 minutes from bleed onset to treatment with NovoSeven®⁸



* Patient-reported outcome study (18 adults and 19 caregivers of 21 children) in which frequently bleeding CHwI patients (>4 bleeds in 3 months) or their caregivers were asked to record bleeding episodes, time of start bleed, symptoms, cause, type, location, time of bleed stop, bypassing agent administered for at least 90 days or until 4 bleeding episodes were reported.¹³

† Dose calculation is based on a recommended individual dose of 90 µg/kg body weight for mild-to-moderate joint, muscle and mucocutaneous bleeds, approximately 5 mg. Dose frequency: 2–3 injections administered at three-hour intervals. If further treatment is required, 1 additional dose of 90 µg/kg body weight can be administered.¹

‡ Post-hoc sub-analysis of SMART-7™ assessed haemostatic response to NovoSeven® in a real world setting where time to first treatment was under 1 hour: a total of 318/618 bleeding episodes treated with rFVIIa monotherapy and with (1) valid efficacy assessment, (2) no missing time for bleed start, (3) no missing time for any dose administration, and (4) valid time to first treatment were included in the analysis. Effective = patient reported that the bleed "stopped"; Partially effective = patient reported that the bleed "slowed"; Ineffective = patient reported that the bleed "worsened / no change".⁸

One solution for many indications in one small box

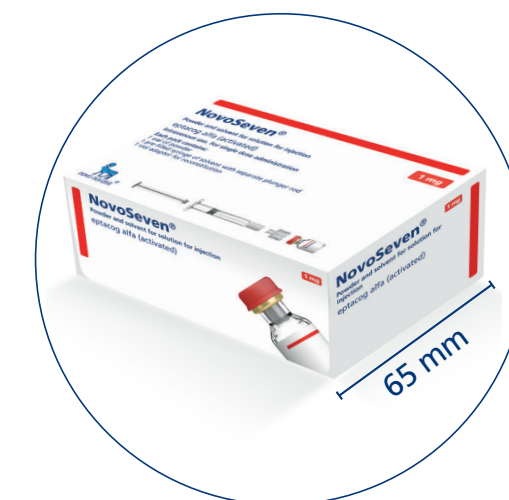
Practical in-hospital storage and easy portability for out-patients

Pre-reconstitution, NovoSeven® is stable for:¹

- up to 3 years at <25°C

Room-temperature stable for portability and easy storage **post-reconstitution**¹

- 6 hours at 25°C
- or 24 hours at 5°C

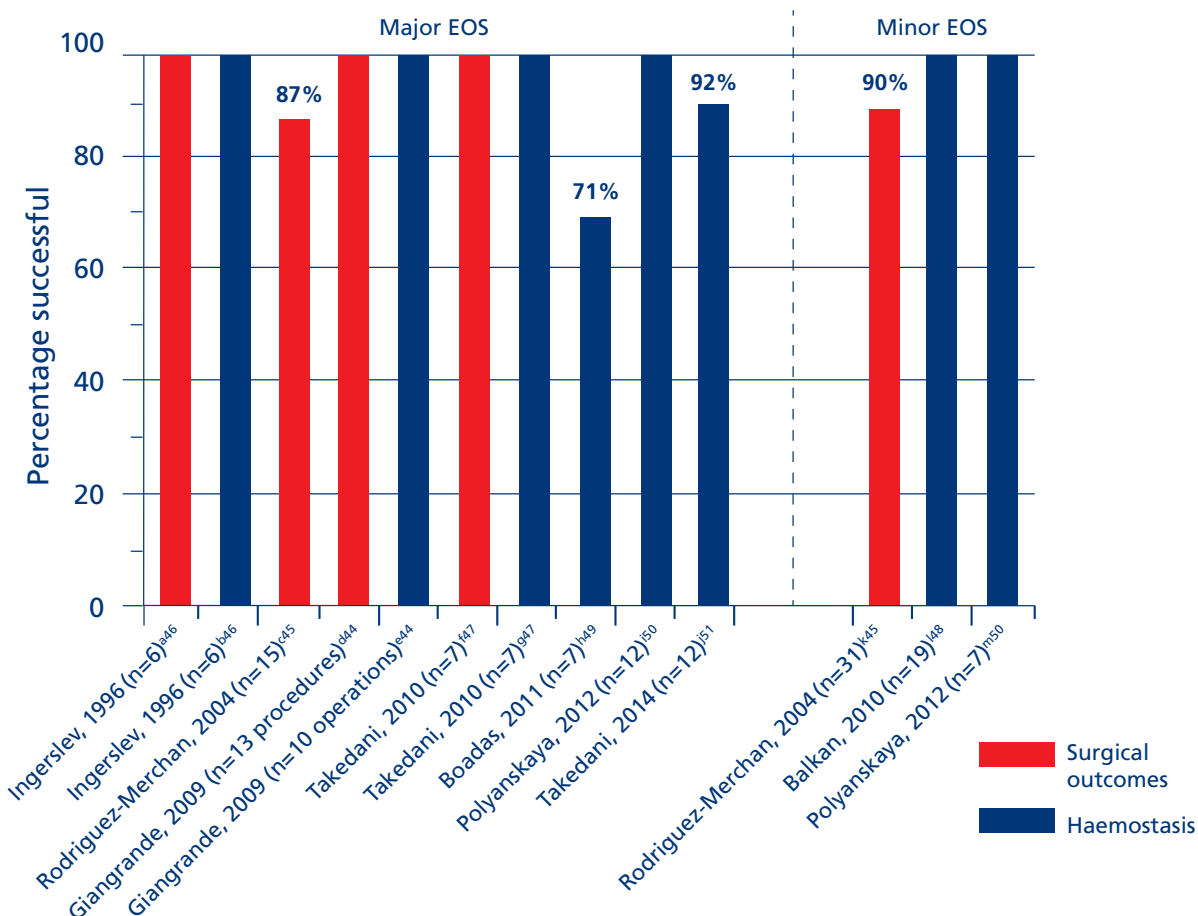


NovoSeven® has 30 years of research and clinical experience across more indications than any other agent^{1,2,14}

	CHAwI	CHBwI	AH	GT	FVIICD	Surgery
NovoSeven® Recombinant Factor VIIa	✓ On-demand	✓ On-demand	✓	✓	✓	✓ Across all indications
FEIBA® ¹⁴	✓ On-demand Prophylaxis	–	✓	–	–	✓ CHAwI and AH

Rely on NovoSeven® for surgical procedures

Reported efficacy of NovoSeven® during major & minor EOS procedures^{*44-51}



This graph illustrates studies identified using the selection and reporting criteria defined below.

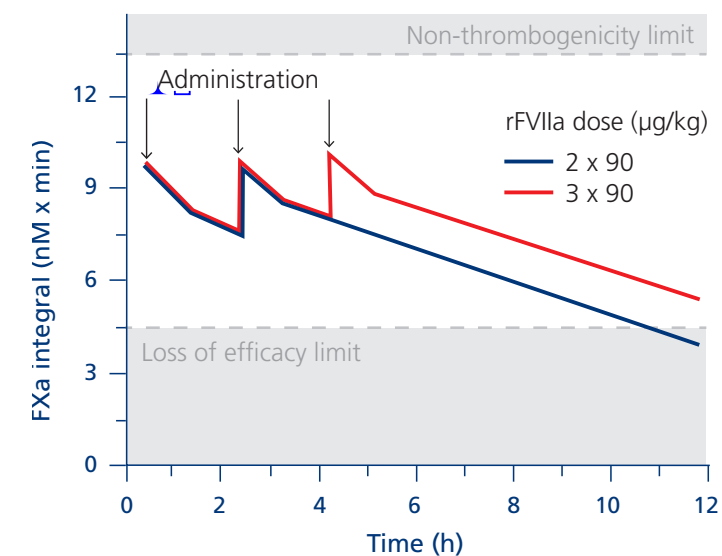
Efficacy shown as percentage successful, defined by the authors as:

- a 'Excellent' or 'efficient' global outcome; missing value excluded
- b Postoperative haemostasis judged as 'achieved'
- c 'Good' or 'fair' outcomes on WFH composite score (pain, bleeding, clinical features, radiological changes)
- d 'Excellent' or 'extremely satisfactory' final outcome
- e 'Satisfactory' intraoperative haemostasis
- f 'Excellent surgical results'
- g No unexpected massive bleeding or bleeding complications
- h Post-operative haemostasis judged 'effective'
- i 'Effective' haemostasis
- j 'Complete haemostasis' (composite score of blood loss, postoperative bleeding control and maintained haemostasis)
- k 'Good' or 'fair' outcomes on WFH composite score (pain, bleeding, clinical features, radiological changes)
- l 'Good' response to treatment (no need for transfusion)
- m 'Effective' haemostasis

* Study selection and reporting criteria

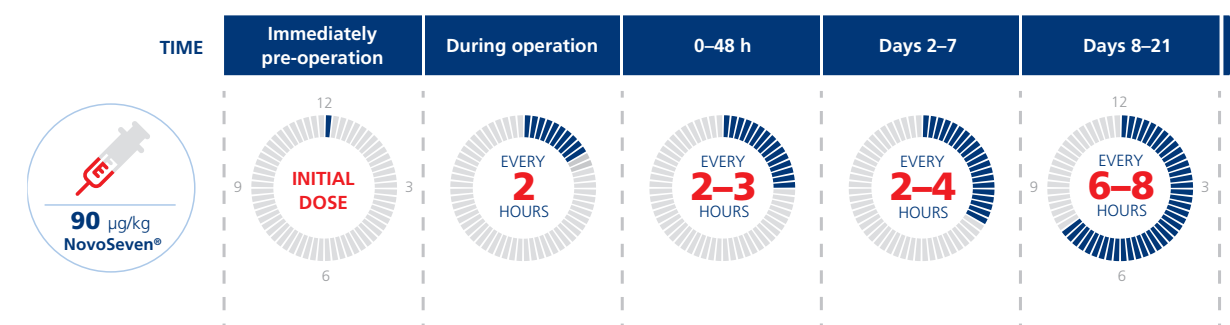
- Reviewed studies reporting ≥ 4 major or minor EOS procedures
- Used the author's definition of minor and major EOS
- Included procedures where outcome of individual procedures could be identified
- rFVIIa used as bolus dose and not in combination with another bypassing agent
- Only EOS procedures reported (non-EOS and pseudotumours excluded)

Possibility to re-dose every 2–3 hours during the surgery and for the (48-hour) immediate post-operative period^{*†52}



Adapted from Shibeko AM et al (2014).⁵²

Dosing for bleed control in surgery¹



More than **400** successful surgical procedures performed with NovoSeven® reported in a range of studies^{44-51,53-67}

* Post-operative bleeding can be a result of inappropriate treatment regimens, which can be resolved by increasing or adding additional doses of bypassing agent.

† It is important to consistently administer NovoSeven® as prescribed as missed or delayed doses can leave patients vulnerable to rebleeds.

1 Start with NovoSeven® when you need rapid bleed control at the hospital¹



Rapid bleed control with consistently high efficacy⁴

- The only bypassing agent with 89%–93% efficacy demonstrated across 4 indications⁴⁻⁸



Favourable safety profile across all approved indications^{2,10,11}

- Established in 30 years of research and experience^{2,10,11}
- Low rate of thrombotic events, due to targeted mechanism of action¹⁰



Rapid reconstitution and administration^{1,12}

- Rapid reconstitution: 5 minutes (median)¹²
- 2–5 minutes to inject¹



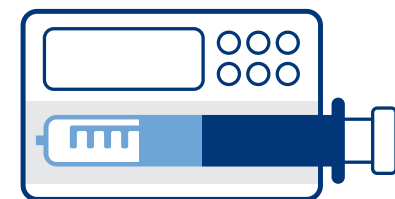
Sid, 27 years old, works for a specialty pharmacy. He enjoys travelling with his fiancée and likes to cook. Sid lives with congenital haemophilia with inhibitors and underwent knee replacement surgery.

2 Stay in control with NovoSeven® through to discharge¹



NEW – NovoSeven® is physically and chemically stable post-reconstitution when stored in a 50 ml syringe (polypropylene) for automated bolus injection for 24 hours at 25°C^{**1,3}

- Specific activity within acceptance criteria³
- Very limited product degradation³
- No changes in transparency, colour or presence of sedimentation³
- No microbiological growth detected³



Bolus doses of NovoSeven® can now be delivered at the hospital by automated bolus infusion pump for the right dose at the right time^{†3}

Administration recommendations according to SPCs (hospital use)^{**1,13,14}

NovoSeven®	Every 2–3 h	Up to every 24 h
	NovoSeven® manual intravenous bolus injections every 2–3 h [†]	Automatic bolus doses every 2–3 h by automated bolus infusion pump ^{1,15} Pump to be replenished once per 24 h ^{‡3,16}
pd-aPCC	Every 12 h	
	Intravenous injection or infusion every 12 h ^{†3}	
Antihemophilic Factor VIII (recombinant), porcine sequence		Every 4–12 h
		Intravenous injection every 4–12 h ^{†4}

* The chemical and physical in-use stability of NovoSeven® has been demonstrated for 24 hours at 25°C in a 50 ml syringe (polypropylene). When administered by pump, a CE-marked infusion pump must be used. All steps for reconstitution and administration should be completed under controlled and validated aseptic conditions by adequately trained personnel. 50 ml polypropylene syringe for automated bolus injection is not provided in the NovoSeven® package. For further details, please refer to 'Procedure for pooling of vials for hospital use only' in the Summary of Product Characteristics.¹

† Any CE-marked pump capable of delivering regular, automated injections can be used via a [50 ml] polypropylene syringe, including hardware already available in hospitals.^{1,3} The pump should be replenished once per 24 h^{1,16} or in accordance with pump manufacturer and hospital guidelines.

** Please consult the relevant SPC for specific dosing in individual indications. Schematics are not drawn to any scale.

‡ Guidelines for replenishing and programming pumps may differ depending on the model used. Please consult your individual hospital's protocol.

NovoSeven[®] administration by automated bolus infusion pump at the hospital can offer a number of benefits^{*†16}



Effective

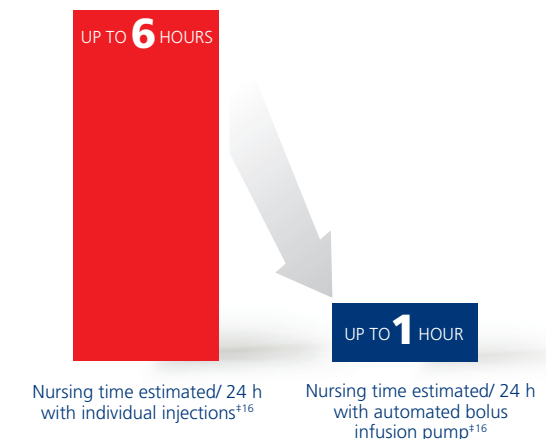
Ensure **consistent efficacy** with the right dose at the right time¹⁶⁻¹⁹

- Delayed or missed doses can leave patients vulnerable to rebleeds¹⁶⁻¹⁹
- Automated administration of the right dose at the right time can give confidence to the MDT that haemostasis will be maintained throughout the procedure^{16,19}

Reduce **burden** of reconstitution and administration for nurses¹⁶

- Reconstitution may only be required once per 24 hour period,^{**16} allowing for a considerable reduction in nursing time with automated administration¹⁶
- Nurse's anxiety about making medication errors can also be decreased¹⁹

Estimated nursing time per 24 h period



Efficient

Effortless

Minimise **disruption** to patients during recovery¹⁶

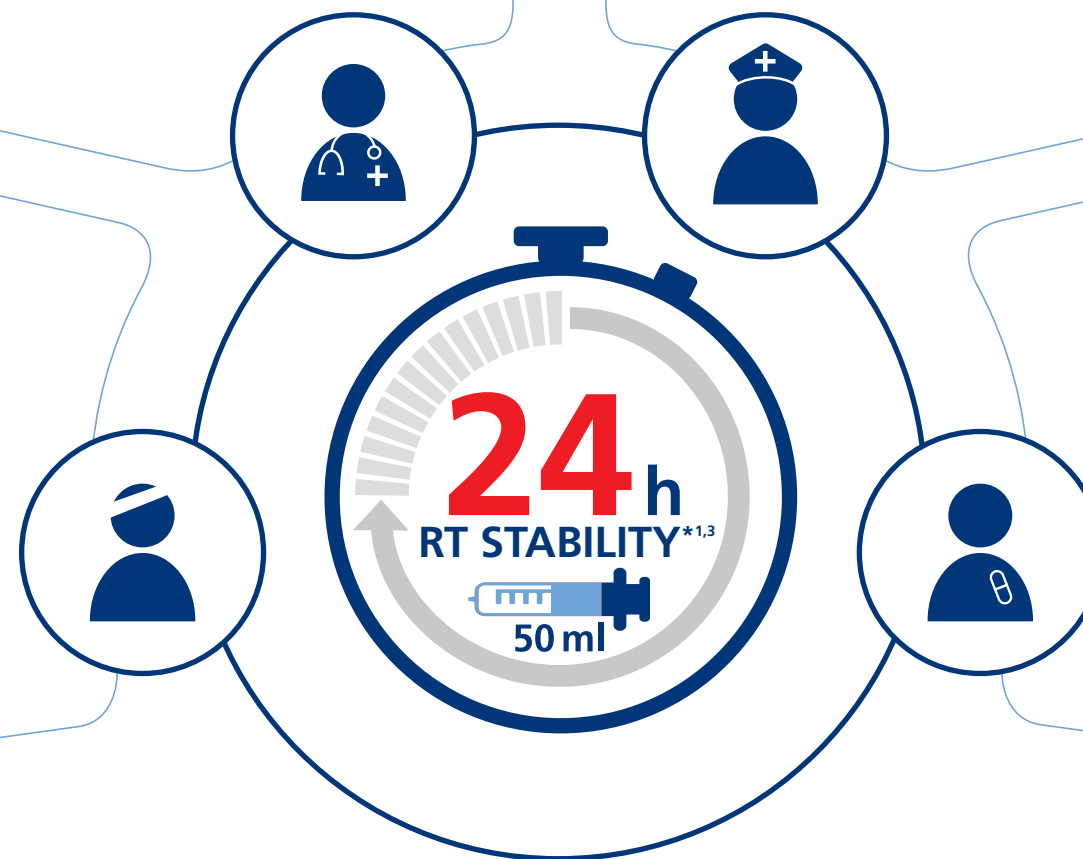
- An automated bolus infusion pump can administer doses throughout the night and avoid waking the patient, supporting rest and recuperation¹⁶

Precise dosing could **reduce overconsumption**¹⁶

- In a study involving two patients receiving NovoSeven[®] via an automated bolus infusion pump post-operatively, savings were estimated at up to 50 mg¹⁶

Up to
50 mg
of savings^{§16}

Economic



* The chemical and physical in-use stability of NovoSeven[®] has been demonstrated for 24 hours at 25°C in a 50 ml syringe (polypropylene). When administered by pump, a CE-marked infusion pump must be used. All steps for reconstitution and administration should be completed under controlled and validated aseptic conditions by adequately trained personnel.¹

† Compared with manual intravenous bolus injections.

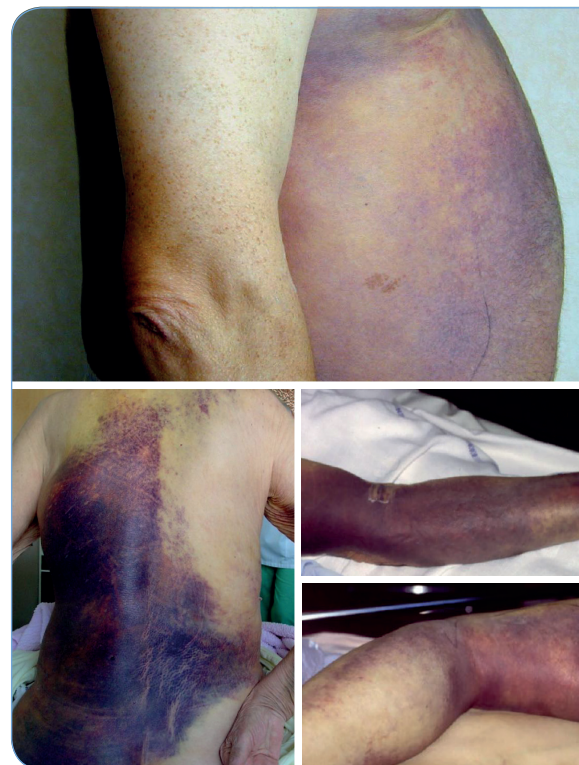
** Guidelines for replenishing and programming pumps may differ depending on the model used. Please consult your individual hospital's protocol.

‡ Total administration time as estimated by Pollard et al. based on 15 minutes of two nurses' time required per dose, representing approximately 6 nursing hours per 24 hours.¹⁶

§ The rounding up of doses when administering individual intravenous bolus injections can result in overconsumption. 50.4 mg overall savings observed across two patients for doses delivered with the automated bolus infusion pump compared with individual manual bolus doses.¹⁶

Acquired haemophilia (AH) can lead to **life-threatening bleeds**^{2,5}

AH occurs when the immune system develops inhibitors for the body's clotting factors, most commonly FVIII²



80%

of patients present with widespread subcutaneous bleeds³

- Other soft tissue and mucosal bleeding is also common³

Extensive subcutaneous bleeding requires **urgent laboratory investigation**^{2,3,6}

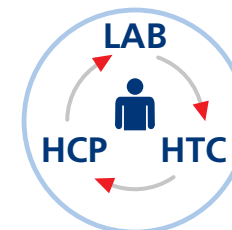
Effective haemostatic treatment can save lives^{5,7}

	Green, 1981 ⁸	EACH2, 2012 ⁵	SACHA, 2013 ⁹	Kruse Jarres, 2015 ¹⁰	HTRS, 2016 ¹¹	ACQUI-7, 2016 ¹²	Jayakar, 2018 ¹³
Patients, n	215	219	82	28	68	27	40
Mortality due to bleeding	22%	3.3%	3.5%	10.7%	0%	3.7%	0%

Your primary treatment objective in AH is to **STOP THE BLEED***

NovoSeven® is a first-choice treatment in AH based on:^{†2,3}

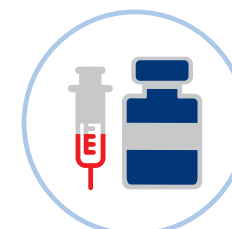
- Rapid bleed control with consistently high efficacy^{5,12,14–19}
- Established safety profile^{1,4,5,20–22}
- Simple, rapid reconstitution and administration[‡] and convenient storage¹



CONSULT:
your laboratory and haemophilia treatment centre (HTC)^{2,3,6}



CONFIRM:
never let a prolonged aPTT go unexplained^{3,6}



CONTROL:
with NovoSeven®¹



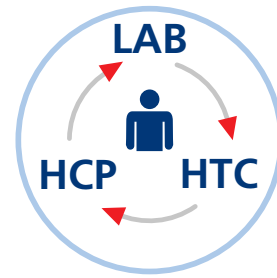
*Published guidelines also recommend eradicating the inhibitor with immunosuppressive therapy.

†Other first-line haemostatic treatments are also recommended.

‡Compared with NovoSeven® vial-to-vial reconstitution 2–5 mins to infuse.

CONSULT:

Urgent laboratory diagnosis is required when unexplained bleeding or bruising occurs^{2,3,6}



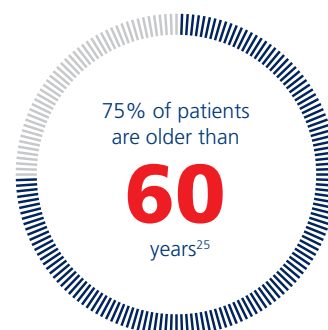
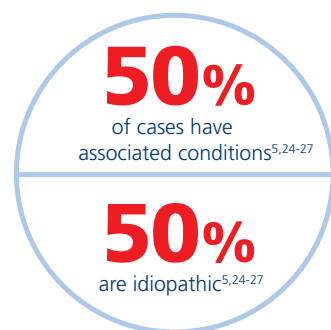
Delays in diagnosis put AH patients at risk of life-threatening bleeds²³

- 33.5% of patients experienced bleeding for >1 week before diagnosis in EACH2²⁴

AH can be difficult to diagnose as patients have no history of abnormal bleeding. Consider AH in patients with:^{2,3}

- Recent onset of abnormal bleeding
- Isolated prolongation in activated partial thromboplastin time (APTT)
- Normal prothrombin time (PT)

AH patient archetypes (impacts both men and women equally):



If you suspect a rare bleeding disorder,
CONSULT your nearest HTC as soon as possible^{2,3,6}



CONFIRM:

Three tests confirm a diagnosis of AH:^{2,3,28–30}

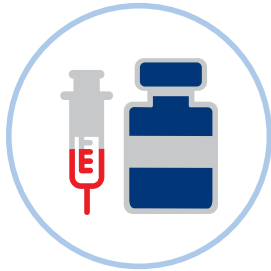


		Abnormal result	Normal range ^{29–31}
1	aPTT Test aPTT mixing test (2 hours incubation at 37°C) Consider pharmacological anticoagulant Consider lupus anticoagulant	Isolated prolonged aPTT >40 seconds	25–40 seconds
2	FVIII:C activity	Low FVIII levels	50–200%
3	Bethesda assay	Presence of FVIII inhibitors	<0.7 BU

Adapted from: Tiede A et al. Semin Thromb Hemost 2014.³²

Always establish the cause of a prolonged aPTT (>40 seconds), irrespective of the clinical presentation^{3,6}

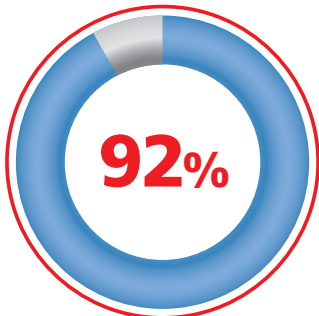
CONTROL:
Stop the bleed with
NovoSeven®¹



- More than 30 years of clinical experience^{1,4}
- More than 1,000 bleeds in 671 patients treated²⁰
- Consistently high efficacy, proven in 6 major registries and studies^{5,12,16–19}



**COMPASSIONATE USE
PROGRAMME IN AH¹⁷**
Multicentre study
1990–1995



JAPANESE PASS¹⁶
Single-centre
post-marketing
surveillance study
2000–2010



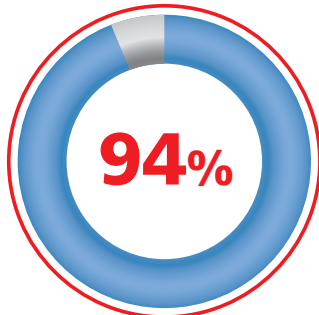
EACH2⁵
European Acquired
Haemophilia Registry
2003–2008



ACQUI-7¹²
Prospective,
observational,
multicentre study
2010–2013



**COMPASSIONATE USE
HRS/HTRS, LITERATURE¹⁸**
Retrospective review of a
longitudinal database
1988–2005



AHS¹⁹
Simple IRB-exempt
case report surveillance
system to supplement
HTRS registry
2008–2011

Key Complete or partial response Bleeds resolved

A median of 36 hours to bleed
resolution with NovoSeven®*⁵

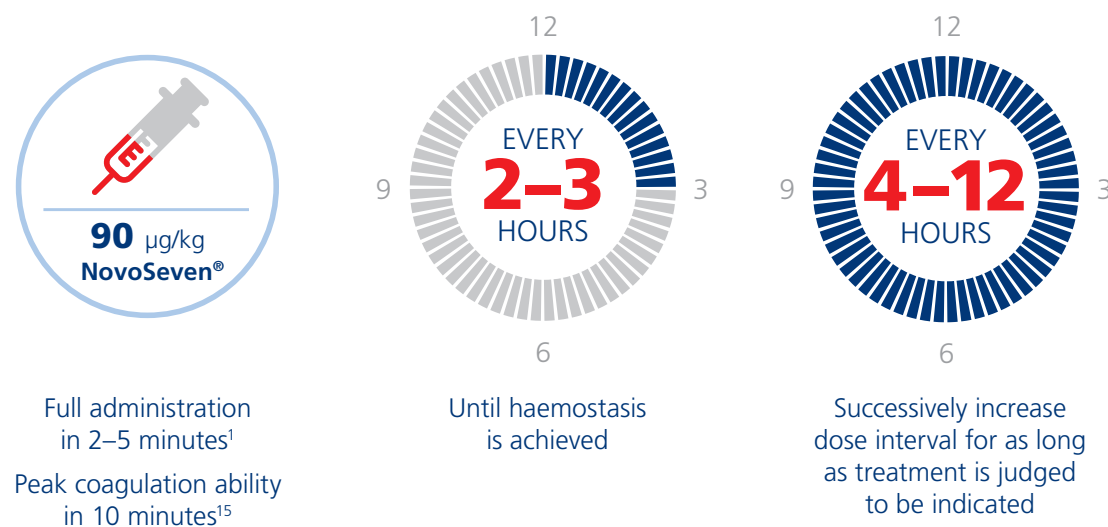
EACH2 dosing of first-line haemostatic therapy for all first bleeding
episodes (median [interquartile range])⁵

	n	Baseline FVIII level, IU/dL	Baseline inhibitor titer, BU/mL	Initial dose, µg/kg or U/kg	Initial dosing interval, hours	Total doses per patient, n	Total dose per patient
NovoSeven [®] Recombinant Factor VIIa	174	2.0 (0.0– 32.0)	15.5 (1.0–2,765)	90 µg/kg (84.71– 102.86)	3 (2–6)	12 (3–35)	84 mg (24– 216 mg)
pd-aPCC	63	1.0 (0.0– 40.0)	18.0 (0.1–1 700)	66.67 U/kg (52.63– 82.19)	12 (12–12)	8 (3–15)	30 000 U (12,000– 56,000 U)

*Median time to bleed resolution based on initial dosing
interval (3 hours) x total doses per patient (12 doses)

NovoSeven® is easy to use, convenient and portable, enabling reconstitution with fewer steps^{*1,33}

NovoSeven® dosing schedule¹



NovoSeven® dose frequency can be adjusted based on severity of bleeding condition and clinical response¹

- No need for real-time monitoring¹
- Allows use of standard laboratory services

^{*}Compared with NovoSeven® vial-to-vial reconstitution.

¹In the hospital setting.

[†]Based on the initial dose for a 56-kg patient with acute bleeding.

Pre-filled syringe, low volume and rapid reconstitution facilitates dosing at the point of care^{*†,1,34,35}

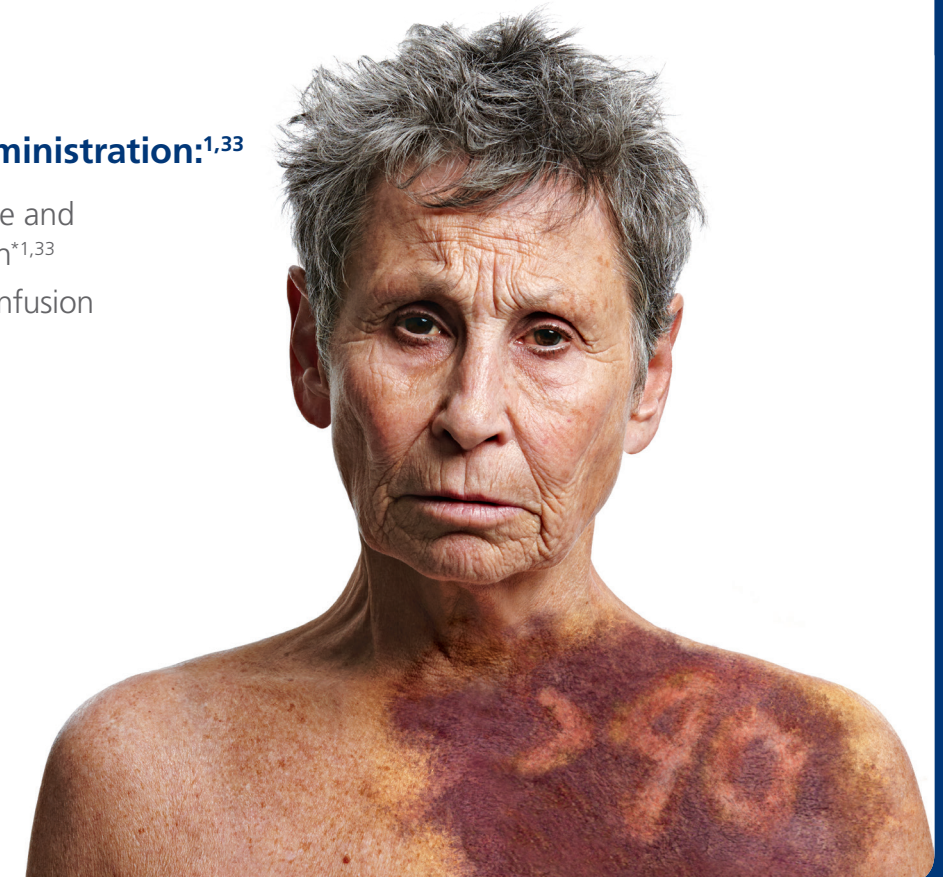


Rapid and convenient administration:^{1,33}

- Pre-filled syringe is easy to use and allows for quick reconstitution^{*1,33}
- Low volume facilitates rapid infusion (2–5 min)¹

Lila, 72 years old, presented with painful swelling in one leg and extensive haematoma. Lila had no prior history of unexplained bleeding.

Model is used for illustrative purposes only.



Favourable safety profile established over 30 years^{1,4,5,7,20–22}

- No risk of transferring blood-borne human pathogens^{4,36}
- Low rate of thrombotic events in a high-risk population (2.9%)^{5,21,37}
- Concomitant treatment with antifibrinolytics is allowed^{1,38}
- Does not induce anamnesis³⁶
- No inhibitory antibodies to NovoSeven® were reported in post-marketing experience¹



Rooted in **RAPID BLEED CONTROL** NovoSeven® has more licensed uses than any other haemostatic drug^{1,5,34,35}

- First and only recombinant bypassing agent^{1,4,36}
- ~5.4 million doses administered since 1996 across all indications²¹

	CHAwI	CHBwI	AH	GT	FVIIcD	Surgery
NovoSeven® Recombinant Factor VIIa	✓ On-demand	✓ On-demand	✓	✓	✓	✓ Across all indications
pd-aPCC³⁵	✓ On-demand prophylaxis	–	✓ On-demand	–	–	CHAwI and AH
rpFVIII³⁴	–	–	✓	–	–	–

CHAwI – congenital haemophilia with inhibitors to coagulation factor VIII; CHBwI – congenital haemophilia with inhibitors to coagulation factor IX; AH – acquired haemophilia; GT – Glanzmann's thrombasthenia; FVIIcD – congenital FVII deficiency.

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Unnecessarily long hospitalisations may incur extra costs⁶

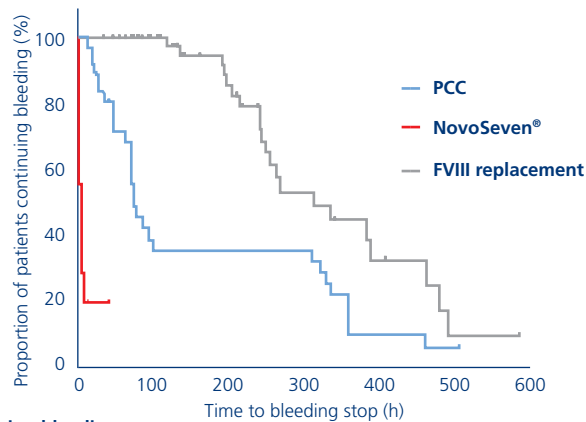
The China Acquired Hemophilia Registry (CARE) was a nationwide multicentre registry in which treatment for acquired haemophilia was assessed⁶



NovoSeven[®] – Cost-effective in first-line treatment of severe bleeds⁵

Because of NovoSeven[®]'s high efficacy and a median time to bleed resolution of 36 hours, the biggest overall drivers of costs are the treatment failures of other therapies when they are used first line instead of NovoSeven[®]^{5,9}

A shorter time to bleed resolution may be cost saving



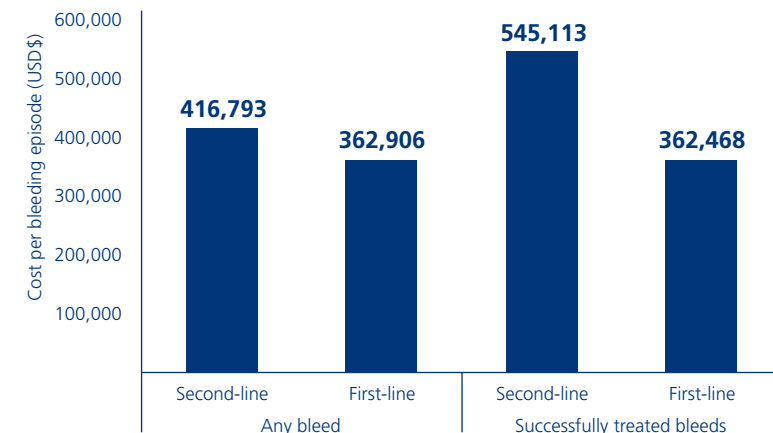
Adapted from Sun 2019.

Data regarding the time to cessation of bleeding was available for 9 patients treated with NovoSeven[®]⁶

- The median time to cessation of bleeding was 5 hours (interquartile range, 2.5–6.75 hours) for patients treated with NovoSeven[®]
- In 2 patients not responding to PCC as initial therapy, bleeding was resolved after receiving NovoSeven[®]
- Of the 40 patients for whom initial FVIII replacement therapy failed, 4 patients received NovoSeven[®] and bleeding was resolved in all of them
 - 23 patients received PCC as salvage therapy, of whom 5 did not respond. Of these 5 patients, bleeding was controlled in 3 with NovoSeven[®]

PCC – prothrombin complex concentrate

Costs per bleeding episode in first- and second-line treatment with NovoSeven[®] in patients with acquired haemophilia⁵



Adapted from Odeyemi and Dano 2008.

- First-line treatment was cost-effective compared with second-line treatment based on an improved efficacy rate (100% vs. 75%) and a reduction of the costs per bleed⁵

* Cost effectiveness study comparing use of NovoSeven[®] first line vs. second line in patients with acquired haemophilia in the US. Costs were calculated based on 2007 USD unit costs.

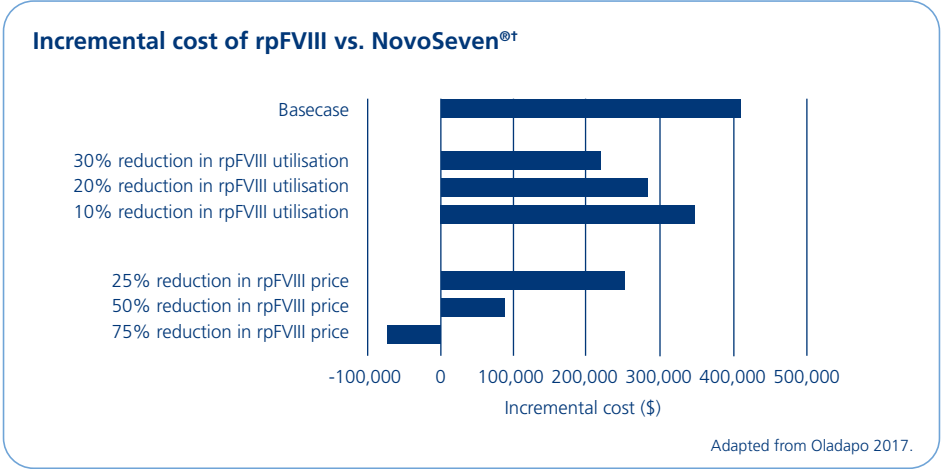
USD – US dollar



NovoSeven® – Cost-effectiveness vs. other options⁷

A simulation model (based on US average sales prices, \$) found that, in a hypothetical cohort of 1,000 patients with AH:^{*7}

	NovoSeven®	rpFVIII
Bleeds controlled in patients initiating with this product	90% (95% CI: 83–96)	90% (95% CI: 79–98)
Estimated discounted lifetime costs	\$264,000	\$672,000
QALYs	6.77 (95% CI: 6.07–7.48)	6.56 (95% CI: 5.38–7.63)



- Inhibitors in acquired haemophilia can cross react with rpFVIII in up to 44% of patients²⁴
- This may result in increased clearance of the product, reduced efficacy and a need for increased product consumption²⁴

* Proportion of patients from the simulated cohort treated with second-line therapy: 39%.

† Results should be interpreted with caution, as sources from which input data were drawn may not be comparable due to differences in methodology, and possible differences in acquired haemophilia A severity and related comorbidities.

AH – acquired haemophilia; CI – confidence interval; QALY – quality-adjusted life year; rpFVIII – recombinant porcine sequence factor VIII



NovoSeven® Abbreviated Summary of Product Characteristics

Consult Summary of Product Characteristics before prescribing.

Presentation: NovoSeven® 1 mg (50 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. NovoSeven® 2 mg (100 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. NovoSeven® 5 mg (250 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. NovoSeven® 8 mg (400 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. **Composition:** eptacog alfa (activated) is recombinant coagulation factor VIIIa (rFVIIa) produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology, 1 mg/vial, 2 mg/vial, 5 mg/vial, 8 mg/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 FVIII deficiency; • patients with Glanzmann's thrombasthenia with post-operative bleeding refractoriness to platelet transfusion available

Posology: Haemophilia A or anamnestic response: Mild to moderate bleeding: Early intervention treatment of mild to moderate bleeding can be achieved with 90 µg per kg body weight at treatment is required, one dose can be administered 2) One dose

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. **Fertility, pregnancy and breast-feeding:** As a precautionary measure, it is preferable to avoid the use of NovoSeven® during pregnancy. 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. Limited data from exposed pregnancies did not show any adverse effect on pregnancy or on the health

of foetus/new-born child. It is unknown whether NovoSeven® is excreted in human breast milk. **Undesirable effects:** The most frequent adverse drug reactions (ADR) are pyrexia and rash (unknown: > 1/1,000 to < 1/100), and the most serious adverse drug reactions are thromboembolic events. The frequency is classified as: Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000) or Not Known. The frequencies of both serious and non-serious adverse drug reactions are listed by system organ class: Blood and lymphatic system disorders: **Rare:** Disseminated intravascular coagulation, related laboratory findings, including elevated levels of D-dimer and decreased levels of Anti Thrombin (AT) and coagulopathy. Gastrointestinal disorders: **Rare:** nausea. General disorders and administration site conditions: **Uncommon:** ADRs are decreased therapeutic response and pyrexia. **Rare:** ADR is injection site reaction including injection site pain. Immune system disorders: Hypersensitivity is **Rare;** anaphylactic reaction frequency is **not known.** Investigations: **Rare:** increased fibrin degradation products, increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Nervous system disorders: **Rare:** headache, skin and subcutaneous tissue disorders: **Uncommon:** Rash (including allergic dermatitis and rash erythematous), pruritus and urticaria. Unknown frequency: flushing and angioedema. Vascular disorders: **Uncommon:** 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, thromboembolic superficial thrombophlebitis and intestinal ischaemia).

Myocardial infarction, cerebral artery occlusion, cerebrovascular al ischaemia, peripheral arterial Angina pectoris. **Unknown:** antibodies: In post-marketing if inhibitory antibodies against haemophilia A or B. In factor antibodies against NovoSeven® and B). Development of inhibitory reported in a post-marketing

observational registry of patients with congenital FVIII deficiency. **Reporting of suspected adverse reactions** after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. **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 FVIII 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. **Administration:** 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 and shelf life:** The shelf life for the product packed for sale is 3 years 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 5°C. From a microbiological point of view, the product should be used immediately. If not used immediately, storage time and storage conditions prior to use are the responsibility of the user, and should not be longer than 24 hours at 2°C - 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. The reconstituted solution should be stored in the vial. **In syringe (50 ml polypropylene) in hospital settings only:** Reconstitution must take place in controlled and validated aseptic conditions by adequately trained staff. Under these conditions, chemical and physical stability has been demonstrated for 24 hours at 25°C when stored in a 50 ml syringe (polypropylene). 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 as stated above. **Procedure for pooling of vials for hospital use only:** During in vitro studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 25°C in a 50 ml syringe (polypropylene). Compatibility with the product was demonstrated for the system consisting of a 50 ml syringe (polypropylene), a 2 m infusion tube (polyethylene) and an in-line filter with a 5 micrometer pore size. The syringe with adequately reconstituted product can be used for administration in a CE-marked infusion pump (accepting a 50 ml syringe), for details on pooling the vials (hospital use only) please refer to the SmPC as of Oct 2019. The infusion pump must only be operated by trained hospital personnel. **Legal category:** Prescription-only medicine (POM). **MARKETING AUTHORISATION NUMBERS:** NovoSeven 1 mg (50 KIU): EU/1/96/006/004, EU/1/96/006/008. NovoSeven 2 mg (100 KIU): EU/1/96/006/005, EU/1/96/006/009. NovoSeven 5 mg (250 KIU): EU/1/96/006/006, EU/1/96/006/010. NovoSeven 8 mg (400 KIU): EU/1/96/006/007, EU/1/96/006/011. **Authorisation holder:** Novo Nordisk A/S, Bagsvaerd, Denmark. **Date of last revision:** October 2019. **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, 8050 Zürich, Switzerland, Tel +41432224300. HQ20NS00010

Consult. Confirm. **CONTROL** with NovoSeven®



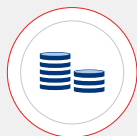
Rapid bleed control with consistently high efficacy⁹⁻¹²



Established safety profile^{1,2,9,13-15}



Simple, rapid reconstitution and administration, and convenient storage^{*1}



NovoSeven® has demonstrated cost-effectiveness

- In the first-line treatment of severe bleeding episodes in patients with acquired haemophilia⁵
- Vs. other options in acquired haemophilia A⁷

Henry, 78 years old, presented with severe and extensive skin bruising and blood in the stool. Henry had no prior history of bleeding.



* Compared with NovoSeven® vial-to-vial reconstitution, 2–5 minutes to infuse.

References: 1. NovoSeven® Summary of Product Characteristics. 2. Hedner U. Blood Rev 2015;29(S1):S4–S8. 3. Huth-Kühne A, et al. Haematologica 2009;94(4):566–575. 4. Collins P, et al. BMC Res Notes 2010;3:161. 5. Odeyemi IA, Dano AM. Value Health 2008;11(6):A633. 6. Sun B, et al. Br J Haematol 2019;187(5):653–665. 7. Oladapo A, et al. Poster PB216 presented at ISTH 2017. 8. Tiede A, et al. Haemophilia 2019;25:969–978. 9. Baudo F, et al. Blood 2012;120(1):39–46. 10. Fernández-Bello I, et al. Haemophilia 2017;23(6):868–876. 11. Amano K, et al. Haemophilia 2017;23(1):50–58. 12. Lentz SR, et al. J Blood Med 2014;5:1–3. 13. Tiede A, Worster A. Ann Hematol 2018;97(10):1889–1901. 14. Neufeld EJ, et al. Haemophilia 2018;24(4):e275–e277. 15. Abshire T, Kenet G. Haemophilia 2008;14(5):898–902. 16. Croom KF, McCormack PL. Biodrugs 2008;22(2):121–136. 17. Tiede A, et al. Blood Rev 2015; 29(S1):S19–S25. 18. Giangrande PL, et al. Haemophilia 2009;15(2):501–508. 19. Neufeld EJ, et al. Blood Rev 2015;29(S1):S34–S41. 20. Obizur® Summary of Product Characteristics. 21. FEIBA® Summary of Product Characteristics. 22. Rexen P, et al. TH Open 2019;3(1):e45–e49. 23. Pollard D, et al. J Haem Pract 2017;4(1):1–5. 24. Turkantoz H, et al. J Thromb Haemost 2020;18(1):36–43.



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Date of preparation: March 2020 HQ20NS00004





EMA label update

Glanzmann's thrombasthenia treatment is moving ahead¹



The European Medicines Agency (EMA)
has extended the label* of NovoSeven® to:^{1†}

- patients with Glanzmann's thrombasthenia (GT) with past or present refractoriness to platelets
- or where platelets are not readily available

Kali, 20 years old, is studying health promotion and likes to do yoga and relax outdoors. Kali lives with Glanzmann's thrombasthenia.

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*In the treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures.

†Previous label stated: NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in patients with Glanzmann's thrombasthenia (GT) with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

NovoSeven®: Rapid bleed control with consistently high efficacy in GT^{11,12}

The European Medicines Agency (EMA) has **extended the label*** of NovoSeven® to:[†]

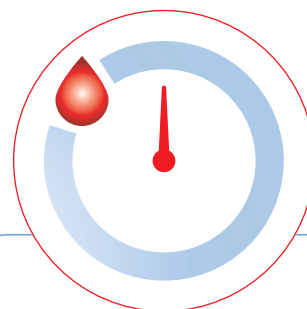
- patients with Glanzmann's thrombasthenia (GT) with past or present refractoriness to platelets
- or where platelets are not readily available



Rapid bleed control with consistently high efficacy for on demand treatment of bleeds and surgery in patients with GT^{11,12}



Favourable safety profile across 30 years of research and experience across all approved indications^{18,19§}



Convenient fast, low volume administration^{1¶}

Cathy, 21 years old, is a huge lover of art and works as a counselor and Arts and Crafts director for the Hemophilia Foundation of Northern California. Cathy lives with Glanzmann's thrombasthenia.



*In the treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures.

†Previous label stated: NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in patients with Glanzmann's thrombasthenia (GT) with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

‡In patients with GT with or without refractoriness.

§Development of NovoSeven® began in June 1985.

¶6 ml in 70 kg 2–5 min bolus infusion.

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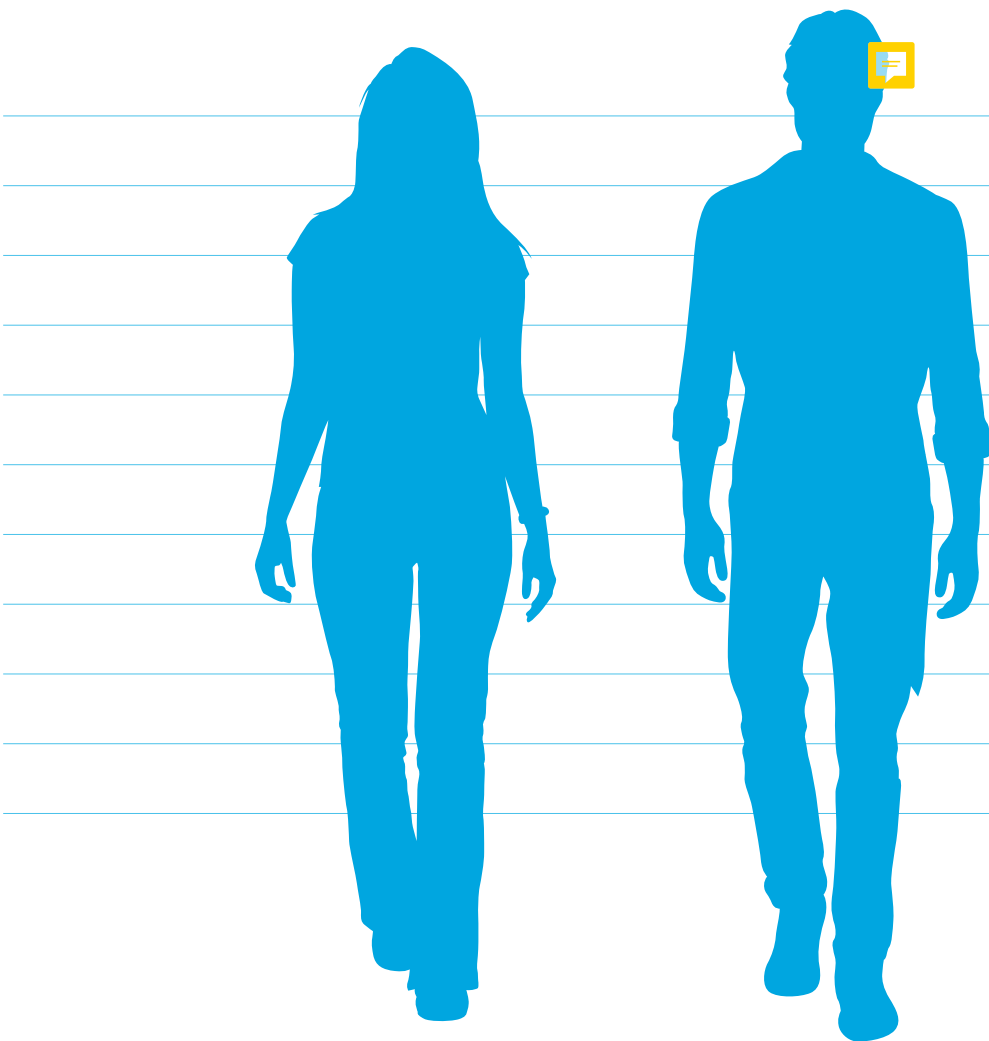
Date of preparation: November 2019.

GT is rare and may be underdiagnosed^{2,3}

GT affects approximately 1 in 1 million people^{4,5}

- GT is a rare platelet function disorder caused by an abnormality in the genes coding for glycoproteins IIb/IIIa⁴
- Glycoproteins IIb/IIIa can be found on the surface of platelet membranes⁵
- The dysfunction or absence of these glycoproteins means that the platelets are unable to effectively aggregate, generating bleeding⁵

Bleeding at different sites is often seen in GT⁶



GT may be difficult to diagnose²

The diagnosis includes:⁵

- Normal platelet count (typically on the lower end of normal)
- Prolonged bleeding time
- Prolonged platelet function assay time
- Platelets fail to aggregate under the conditions utilised in the light transmission aggregometry test

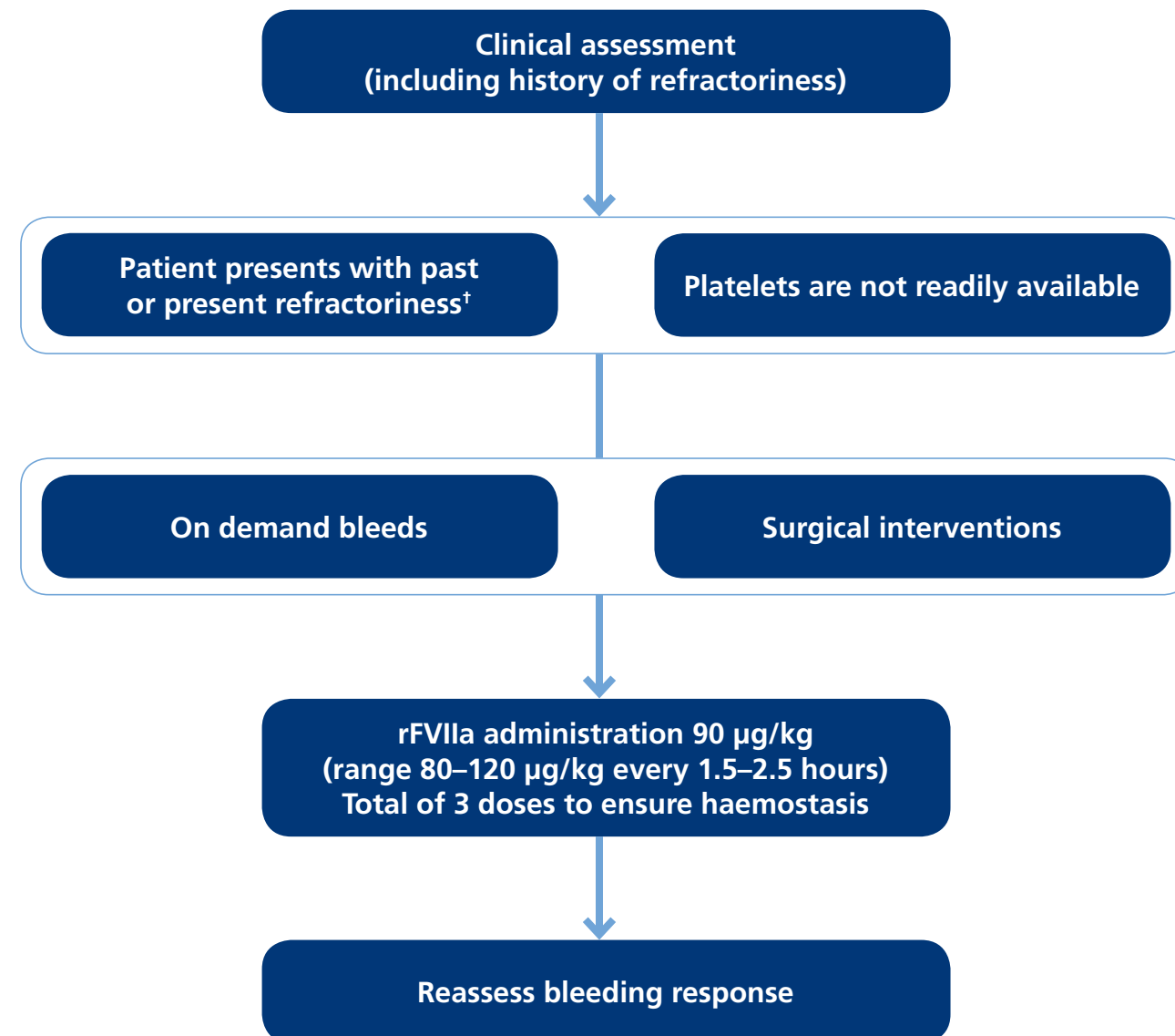
67%	Epistaxis
60%	Circumcision surgery*
58%	Easy bruising
56%	Dental procedures
44%	Gum bleeding
22%	Menorrhagia†
21%	Gastrointestinal/intra-abdominal bleeding
14%	Haematuria
12%	Muscle
9%	Ear bleeding
9%	Haematoma
7%	Trauma

Percentages represent the proportion of patients (total=43) with GT experiencing each type of bleeding episode in a retrospective survey.⁶

GT=Glanzmann's thrombasthenia. GPIIb-IIIa=glycoprotein IIb-IIIa.
*Surgery=circumcision in 12/20 male subjects.
†Menorrhagia=5/23 female patients who had attained the age of menarche.

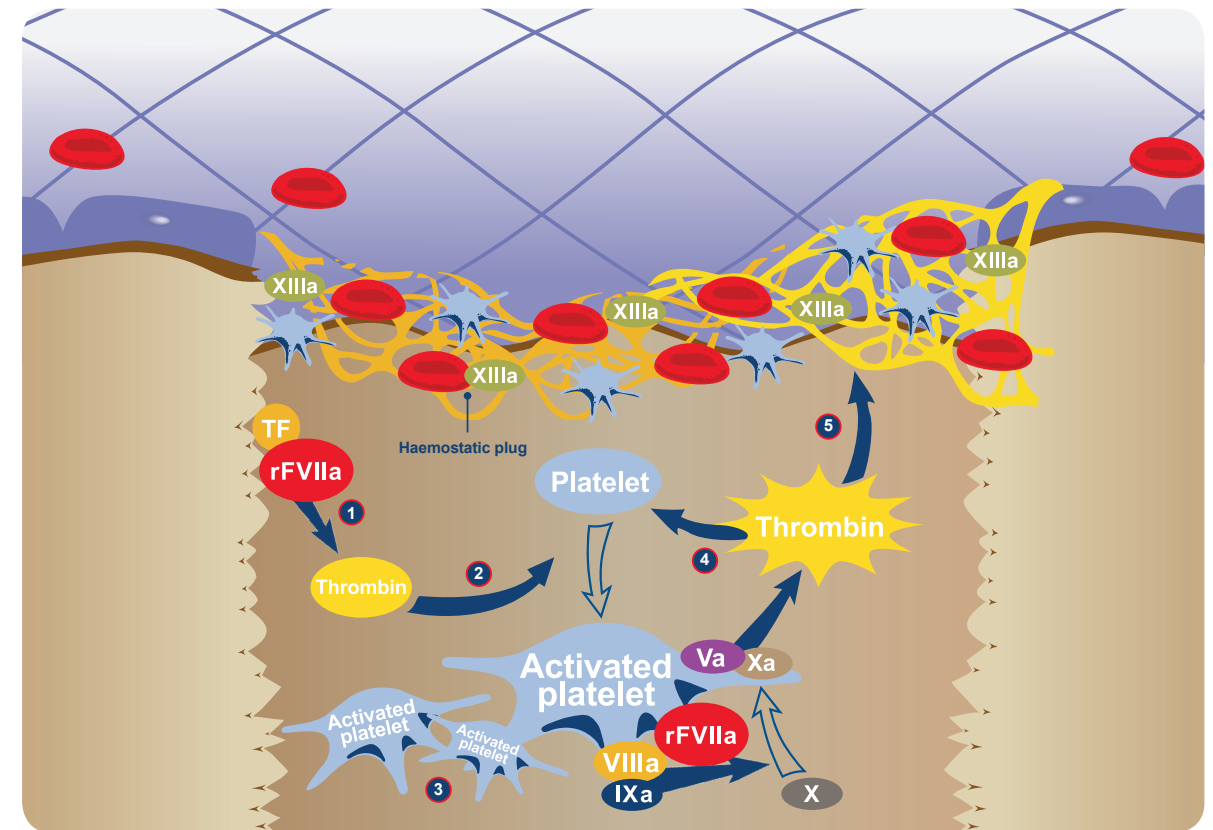
GT=Glanzmann's thrombasthenia.

NovoSeven® supports your GT patients with past or present refractoriness or when platelets are not readily available^{1*}



GT=Glanzmann's thrombasthenia; rIIVa=recombinant factor IIa.
 *Hypothetical treatment pathway – based on the EMA label update.
 †For those patients who are not refractory, platelets are the first line treatment for Glanzmann's thrombasthenia.

NovoSeven® provides a fast-acting, uniquely targeted mode of action in GT^{7–10}



- 1 NovoSeven® enhances local TF-dependent thrombin generation^{7,8,10}
- 2 High levels of NovoSeven® increase the likelihood of platelet activation...^{7,10}
- 3 ...and may also enhance GPIIb-IIIa-independent platelet aggregation⁹
- 4 NovoSeven® can bind to platelets via TF-receptor GPIIb or directly to the partially activated platelet surface and increase the likelihood of thrombin generation and platelet activation¹⁰
- 5 NovoSeven® increases local fibrin deposition at the site of injury,⁷ contributing to effective clot formation and helping to stop the bleed

GPIIb=glycoprotein IIb; GPIIb-IIIa=glycoprotein IIb-IIIa; GT=Glanzmann's thrombasthenia;
 HLA=human leukocyte antigen; TF=tissue factor.

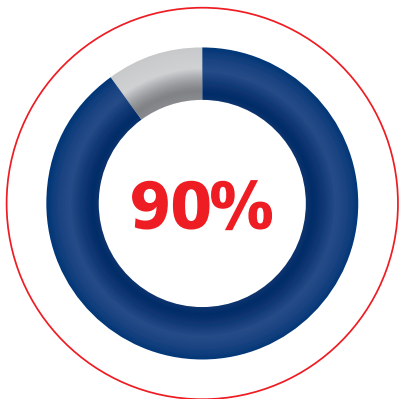
Please see abbreviated Summary of Product Characteristics on page 11 of this brochure.



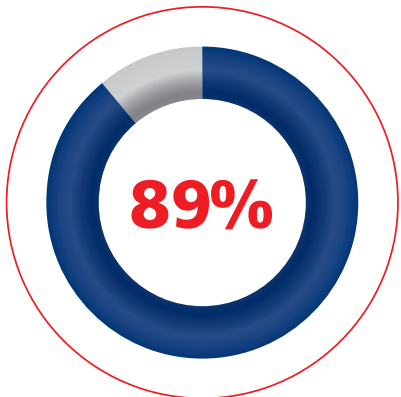
NovoSeven® provides rapid bleed control with consistently high efficacy in GT^{11,12}

Results from the GT Registry demonstrated **consistent high efficacy** of NovoSeven® in the treatment of bleeding episodes and prevention of bleeds in surgery in patients with GT^{11,12*}

Treatment of bleeding episodes¹¹



Effective in GT without refractoriness or antibodies^{11†}

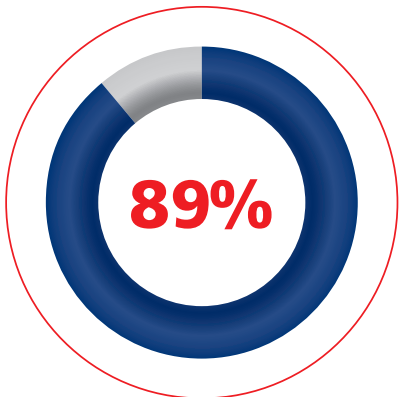


Effective in GT with refractoriness^{11†}

Prevention of bleeds in surgery¹²



Effective in GT without refractoriness or antibodies^{12‡}

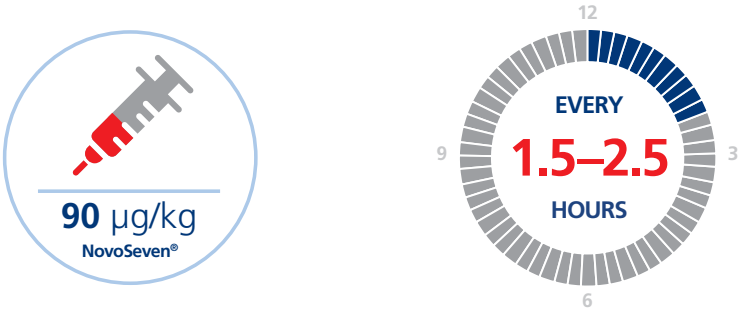


Effective in GT with refractoriness^{12‡}

GT=Glanzmann's thrombasthenia.
 *The GTR is an observational registry (F7HAEM-3521) covered 133 subjects with Glanzmann's thrombasthenia treated with NovoSeven®. The median dose per infusion for treatment of 333 bleeding episodes was 90 µg/kg (range 28 to 450 µg/kg). NovoSeven® was used in 157 surgical procedures, at a median dose of 92 µg/kg (up to 270 µg/kg). Treatment with NovoSeven®, alone or in combination with antifibrinolytics and/or platelets, was defined as effective when bleeding was stopped for at least 6 hours. All surgeries were minor and all bleeds were moderate in severity.
 †Used alone not in combination with other treatments.
 ‡Used alone not in combination with other treatments. All surgeries were minor.

NovoSeven® provides convenience for home- and hospital-based treatment^{1,13,14}

It is recommended to administer at least 3 doses of NovoSeven® to secure effective haemostasis.¹



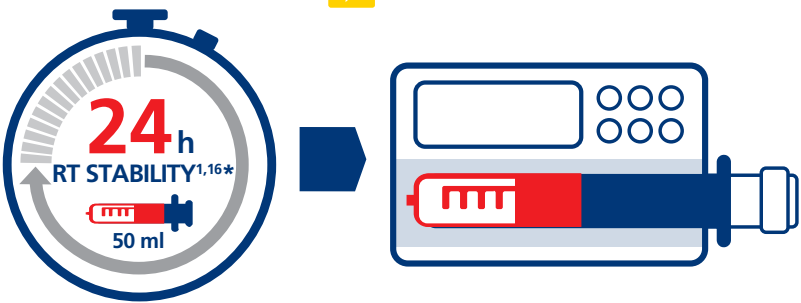
Convenient for home-based treatment

- Fast and convenient reconstitution with pre-filled syringe and broad range of vial sizes^{1,15}
- Rapid administration in 2–5 minutes¹
- Portable and easy to store with 3 years' stability at <25°C¹



Convenient for hospital-based treatment

- NovoSeven® is physically and chemically stable post-reconstitution when stored in a 50 ml syringe (polypropylene) for automated bolus injection for up to 24 hours at 25°C^{1,16*†}
- Bolus doses of NovoSeven® can now be delivered at the hospital by automated bolus infusion pump for the right dose at the right time^{16†}



RT=room temperature.
 *In-use stability of NovoSeven® has been demonstrated for 24 hours at 25°C in a 50 ml syringe (polypropylene). 50 ml polypropylene syringe not provided in the NovoSeven® package. For further details, please refer to the Summary of Product Characteristics.¹
 †Any CE-marked pump capable of regular, automated injections can be used via a 50 ml polypropylene syringe, including hardware already available in hospitals.^{1,16} The pump should be replenished once per 24 h,^{1,17} or in accordance with appropriate guidelines.
 Please see abbreviated Summary of Product Characteristics on page 11 of this brochure.



NovoSeven®: **Rapid bleed control** with consistently high efficacy

In congenital factor VII deficiency (cFVIIID)^{1,2}

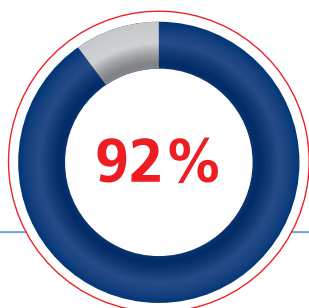
Taylor, 20 years old, is studying history and plans to go to law school. She enjoys sewing and loves to do ballet. Taylor lives with congenital factor VII deficiency



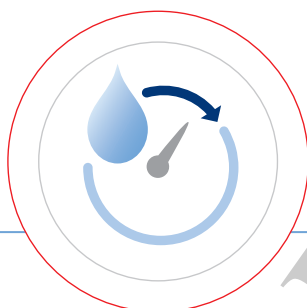
This material is a **DRAFT** for preparatory **internal use in Novo Nordisk only**. Affiliates are responsible for reviewing the promotional material against local label, more stringent relevant local legislation, and if relevant, local code of conduct (cf. S.O.P. 100965 Approval of Promotional Material in Novo Nordisk) before distribution.

NovoSeven®: **Rapid bleed control** with consistently high efficacy

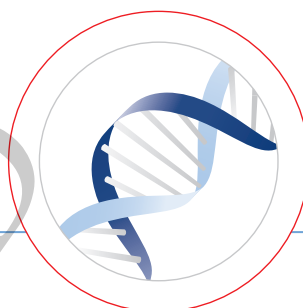
In congenital factor VII deficiency (cFVIIID)^{1,2}



Rapid bleed control with consistently high efficacy^{2,19}



Fast, low volume administration¹⁵



Favourable safety profile using recombinant technology^{15,22,24}

Xavier, 6 years old, loves swimming, cycling, playing outside and cooking with his mum. Xavier lives with congenital factor VII deficiency.



Please see abbreviated Summary of Product Characteristics on page 9 of this brochure.

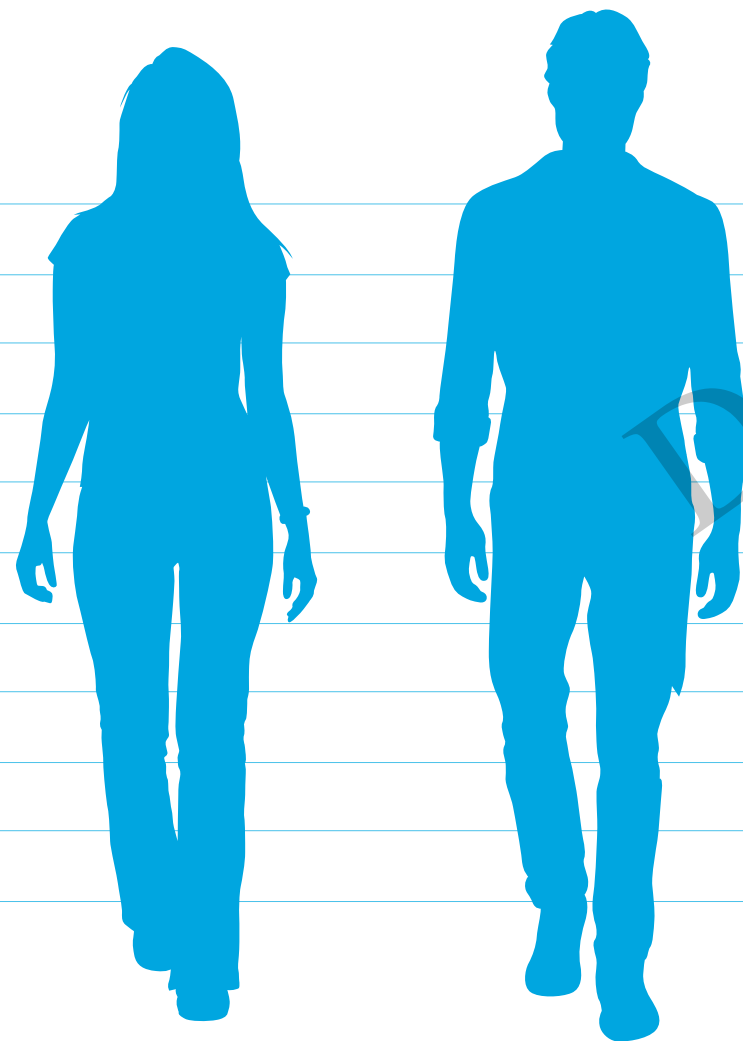
NovoSeven® is a registered trademark owned by Novo Nordisk® Health Care AG. © 2020 Novo Nordisk Healthcare AG, Zurich, Switzerland. HQ20NSVN00003
Date of preparation: January 2020.

Congenital factor VII deficiency (cFVIIID) is the most common of the rare congenital coagulation disorders^{3,4}

cFVIIID affects approximately 1 individual in every 500,000 and may be underdiagnosed⁵

- cFVIIID is a rare autosomal recessive coagulation disorder⁴
- It affects men and women equally⁶
- There are a wide range of clinical phenotypes, ranging from serious haemorrhagic episodes to an asymptomatic condition²
- 44% of cFVIIID patients are asymptomatic⁷

Characteristic bleeding sites in symptomatic patients with cFVIIID⁷



Pathophysiology of cFVIIID

- cFVIIID is characterised by a deficiency or dysfunction in FVII⁸
- Following injury, only a limited amount of the FVIIa:TF complex is produced⁹. This impairs thrombin-mediated platelet activation and compromises formation of a stable haemostatic plug¹⁰⁻¹⁴

22% Epistaxis

11% Menorrhagia*

6% Central nervous system

5% Ecchymoses

4% Gum

3% Gastrointestinal

3% Haemathrosis

3% Haematomas

2% Umbilical

1% Haematuria

1% Rectal†

1% Other

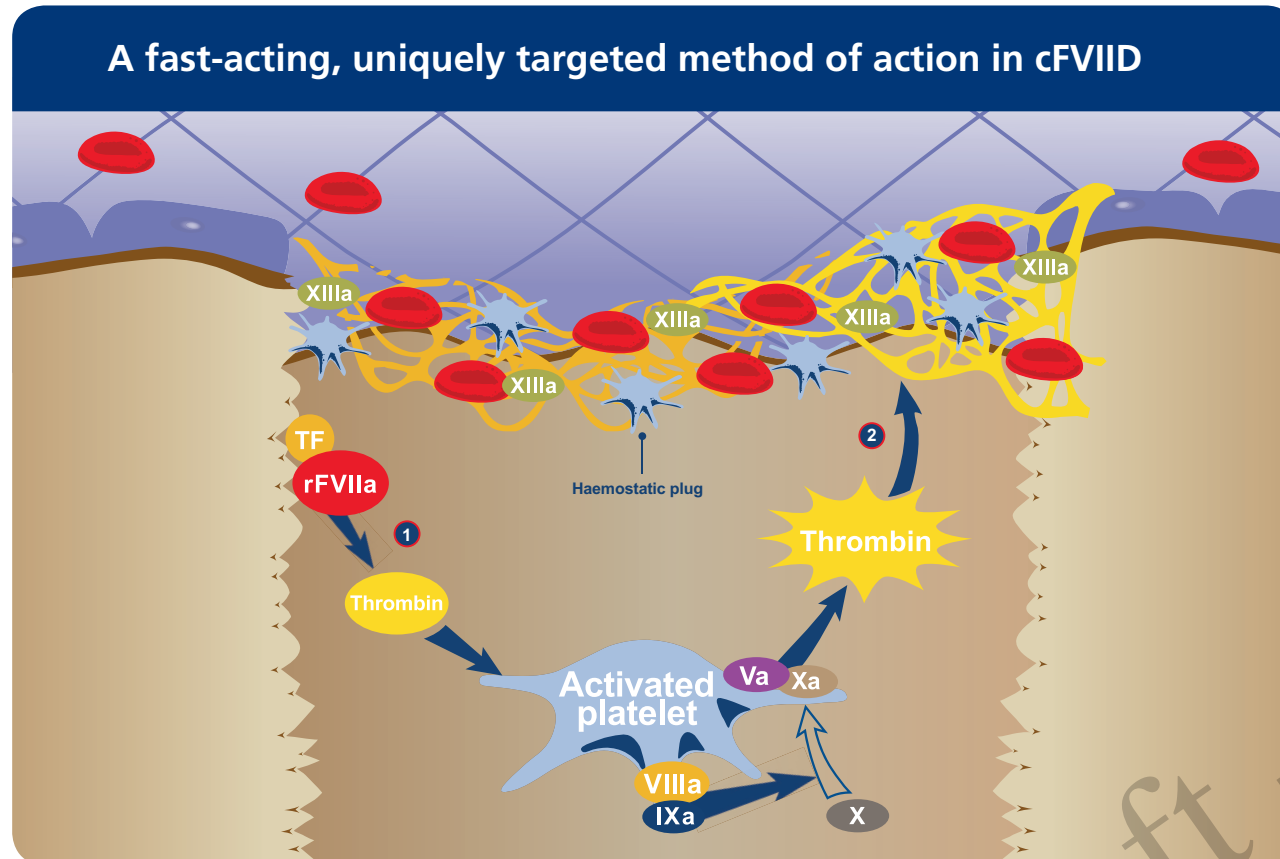
Percentages represent the proportion of patients (total=626) with cFVIIID experiencing each type of bleeding episode in a retrospective registry.

*Menorrhagia=in all 36/325 female patients.

†Rectal=mostly haemorrhoidal.

FVIIa=activated factor VII; TF=tissue factor.

NovoSeven® supports your patients with congenital factor VII deficiency (cFVIID)¹⁵

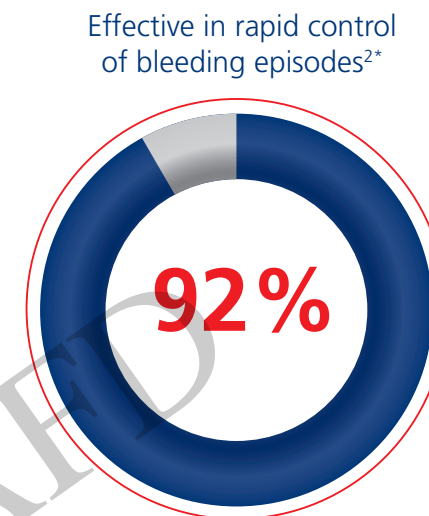


- 1 NovoSeven® replaces missing endogenous FVIIa, leading to the initiation of coagulation.^{4,16,17} However, if tissue factor (TF) is not exposed (i.e. there is no injury), NovoSeven® is cleared from the plasma¹⁸
- 2 Replacement of the missing FVII with NovoSeven® results in the formation of a stable haemostatic plug¹⁴

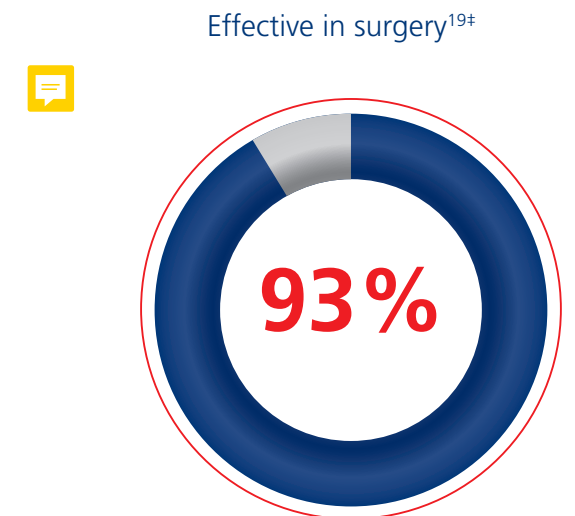
Please see abbreviated Summary of Product Characteristics on page 9 of this brochure.

NovoSeven® provides rapid bleed control with consistently high efficacy in cFVIID^{1,2}

In the STER:



- 71% of patients reported that bleeds stopped with 1–2 doses^{2†}



- No bleeding episodes reported:**
- In 17 out of 17 minor surgeries¹⁹
 - In 21 out of 24 major surgeries¹⁹

STER^{2,19,20}

A multi-centre, prospective, observational, web-based registry to collect and describe treatment modalities and outcomes in cFVIID

- Data collected for 8 years (2004–2012)
- Includes 41 elective surgeries in 34 patients treated with NovoSeven^{®19}
- Includes 101 bleeds evaluated in 75 patients; 79/101 bleeds treated with NovoSeven^{®2}

STER=Seven Treatment Evaluation Registry.

*Bleed control at 6 hours was rated "excellent" (single administration leads to cessation of overt bleeding, pain relief and reduced swelling) or "effective" (more than one administration needed for same symptoms) for 73 of 79 (92%) bleeds in patients with cFVIID.

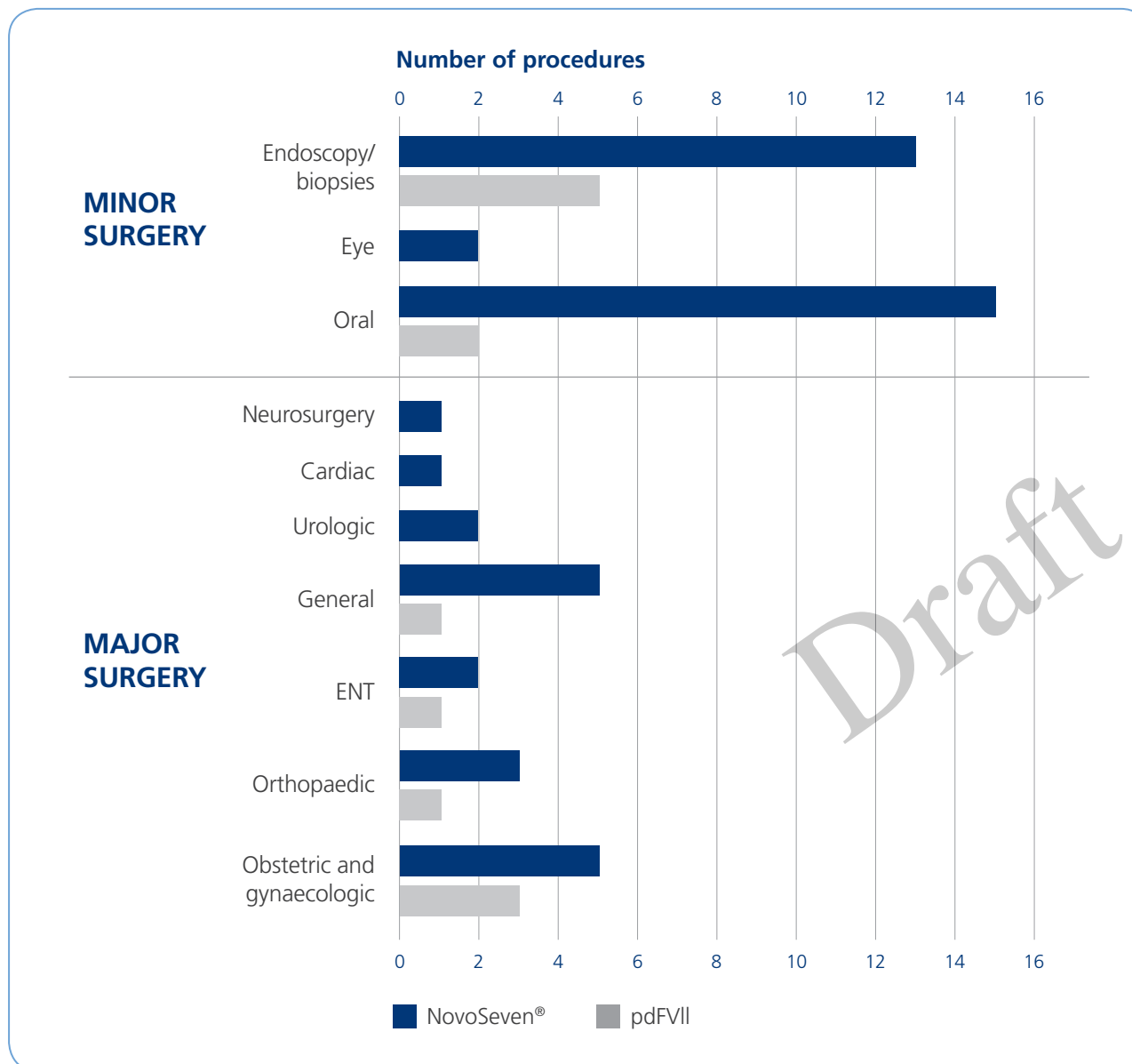
†In treatments considered "excellent" or "effective" (49 of 69 patients, 71%), bleeding could be stopped with 1–2 doses.

‡Bleed control 'effective' (no bleeding episodes reported).

NovoSeven® is well established for use in surgery in women with congenital factor VII deficiency (cFVIIID)²¹

- Bleeding in women with cFVIIID is mainly characterised by mucocutaneous bleeding, also resulting in gynaecological and obstetric challenges to haemostasis²¹
- NovoSeven® was used as replacement therapy in 50/63 (79%) surgeries in women with cFVIIID²¹

Surgical procedures in women with cFVIIID: New data²¹

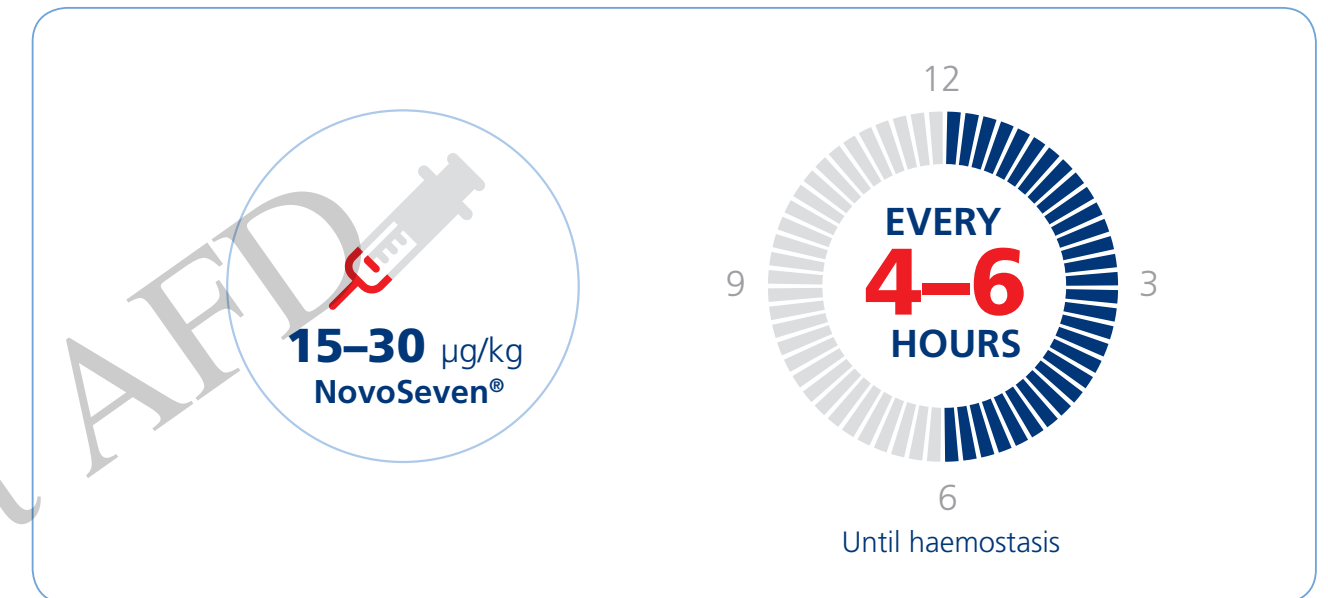


- The graph shows the number of surgical procedures (major and minor) in women with cFVIIID treated with NovoSeven® or pdFVII

ENT=ear, nose and throat; pdFVII=plasma-derived FVII.

Please see abbreviated Summary of Product Characteristics on page 9 of this brochure.

NovoSeven® provides flexible dosing for bleed control and prevention of bleeding in surgery or invasive procedures^{15†}



Barbara, 65 years old, enjoys a full life living on a farm and running an antique stall. She is also a volunteer Patient Advisor at her local hospital. Barbara lives with congenital factor VII deficiency.

[†]Dose and frequency of injections should be adapted to each individual

Committed to create the best care environment

Ongoing focus

Novo Nordisk is largely governed by the **Novo Nordisk Foundation**, whose formal purpose is to provide a stable basis for its company's operations and to make contributions to scientific, humanitarian and social progress.⁶⁸

Educational programmes and research support aim to improve knowledge about **joint health** and the understanding of **psychosocial issues**.⁶⁹

Through **partnerships** and **advocacy**, Novo Nordisk influences social, economic and political environments to help raise awareness and improve patient care.⁶⁹

Product portfolio

Novo Nordisk has an established portfolio of treatments for haemophilia and other bleeding disorders.^{1,68,70-72}

NovoSeven®
Recombinant Factor VIIa

novoeight®
turoctocog alfa

refixia®
nonacog beta pegol

novothirteen®
catridecacog



Bob, 63 years old,
enjoys playing the guitar,
fishing and boating with his
wife. Bob lives with congenital
haemophilia with inhibitors.

Abbreviated Summary of Product Characteristics

NovoSeven® 1 mg (50 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. NovoSeven® 2 mg (100 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. NovoSeven® 5 mg (250 KIU) powder and solvent (vial or pre-filled syringe) for solution for injection. NovoSeven® 8 mg (400 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, 2 mg/vial, 5 mg/vial, 8 mg/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'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 experience with administration of a single dose of 270 µg per kg

Serious bleeding episodes: An initial dose of 90 µg per kg body weight should be administered on the way to the hospital where the following dose varies according to the type and severity of the haemorrhage. The first dose should initially be every second hour until clinical improvement is observed. If no improvement is observed, the dose interval can then be increased to 3 hours for mild to moderate bleeding and to 4, 6, 8 or 12 hours for severe bleeding as indicated. A major bleeding episode may be treated with a single dose of 270 µg per kg body weight. If bleeding persists, the dose interval 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:** The most frequent adverse drug reactions (ADR) are pyrexia and rash (uncommon: > 1/1,000 to < 1/100), and the most serious adverse drug reactions are thromboembolic events. The frequency is classified as: Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000) or Not Known. The frequencies of both serious and non-serious adverse drug reactions are listed by system organ class: Blood and lymphatic system disorders: *Rare:* Disseminated intravascular coagulation, related laboratory findings, including elevated levels of D-dimer and decreased levels of Anti Thrombin (AT) and coagulopathy. Gastrointestinal disorders: *Rare:* nausea. General disorders and administration site conditions: *Uncommon:* ADRs are decreased therapeutic response and pyrexia. *Rare:* ADR is injection site reaction including injection site pain. Immune system disorders: Hypersensitivity is *Rare;* anaphylactic reaction frequency is *not known.* Investigations: *Rare:* increased fibrin degradation products, increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Nervous system disorders: *Rare:* headache, skin and subcutaneous tissue disorders: *Uncommon:* Rash (including allergic dermatitis and rash erythematous), pruritus and urticaria. Unknown frequency: flushing and angioedema. Vascular disorders: *Uncommon:* 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). *Rare:* 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. *Unknown:* Intracardiac thrombus. **Inhibitors:** No reports of inhibitory antibodies against NovoSeven® or FVII in patients with haemophilia A or B. Formation of antibodies against NovoSeven® and FVII is the development of inhibitory antibodies to NovoSeven® has been monitored in a national registry of patients with congenital FVII deficiency. **Reactions:** After authorisation of the medicinal product is marketed, the benefit/risk balance of the medicinal product is monitored. 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. **Administration:** 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. 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. **Way of delivery:** Medical prescription. **Authorisation holder:** Novo Nordisk A/S, Bagsvaerd, Denmark. **Date of last revision SMP:** December 2016. **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, 8050 Zurich, Switzerland, Tel +41432224300. **Date of preparation:** November 2017. HQMMA/N7/0616/0086(1)

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