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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

NovoSeven® RT: **Success speaks for itself**

Proven effective for bleed resolution and surgery across 4 indications[2]
- CHAwI, CHBwI, AH, GT, and CFVIId

A well-established safety profile
- Low rate of thrombotic events based on clinical trials and registry data[2]
  - 0.2% in CHwI bleeds, 4% in AH patients, <0.2% in GT bleeds

Not made from human serum or human proteins[2]

Able to quickly treat bleeds when they occur
- Rapid administration and infusion, leading to rapid activity[2,3]

With NovoSeven® RT, the experience continues
- >30 years of clinical experience[3,a]

CHwI=congenital hemophilia with inhibitors; CHAwI=congenital hemophilia A with inhibitors; CHBwI=congenital hemophilia B with inhibitors; AH=acquired hemophilia; CFVIId=congenital factor VII deficiency; GT=Glanzmann's thrombasthenia.

[a]1988: compassionate use initiated in the United States; 1999: FDA approval received for CHwI.[2,5]

Indications and Usage

NovoSeven® RT (coagulation Factor VIIa, recombinant) is a coagulation factor indicated for:

- Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and perioperative management in adults with acquired hemophilia

Important Safety Information

WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

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NovoSeven® RT **helps a broad range of patients[b]** with bleeding disorders[2]

bleed treatment | perioperative management

Indications	NovoSeven®RT[2,c]	FEIBA® [6,d]	Obizur®[7,e]	SevenFACT®[8,f,g]
Congenital hemophilia A with inhibitors	bleed treatment, perioperative management	bleed treatment, perioperative management		bleed treatment
Congenital hemophilia B with inhibitors	bleed treatment, perioperative management	bleed treatment, perioperative management		bleed treatment
Acquired hemophilia	bleed treatment, perioperative management		bleed treatment	
Congenital factor VII deficiency	bleed treatment, perioperative management			
Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets	bleed treatment, perioperative management			

[b]Indicated for bleed control and surgery in 4 bleeding disorders.[2]
[c]NovoSeven®RT is a recombinant FVIIa.
[d]FEIBA is an activated prothrombin complex concentrate (aPCC).
[e]Obizur is a porcine sequence recombinant FVIII.
[f]SevenFACT is a recombinant FVIIa.
[g]SevenFACT is only indicated for adults and adolescents (12 years and older).

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

NovoSeven® RT **is there for your patients when bleeds happen**

A well-established safety profile, with >30 years of clinical experience[4]

Clinical trials[2]

Occurrence of thrombotic events in CHwI bleeding episodes

MASAC recommends rFVIIa to treat acute bleeds in patients with congenital hemophilia A with inhibitors taking emicizumab prophylaxis[9]

During the HAVEN studies, in patients receiving emicizumab prophylaxis:

- **47% of bleeds** were treated with a single injection of NovoSeven® RT in HAVEN1[10,a]
- **No serious AEs and no cases of TMA or TE** were associated with the use of NovoSeven® RT alone in HAVEN1, 2, and 4[10]
- **Two cases of TMA** occurred in patients receiving FEIBA and NovoSeven® RT. Simultaneous use of NovoSeven® RT and FEIBA should be avoided[11]

MASAC=Medical and Scientific Advisory Council; rFVIIa=recombinant activated factor VII; TE=thrombotic event; TMA=thrombotic microangiopathy.
[a]The analysis included bleeding episodes in the HAVEN1, HAVEN2, and HAVEN4 clinical trials for which patients with CHAwI on emicizumab prophylaxis (at the labeled dose) used rFVIIa. Initial individual dosing with rFVIIa, dosing intervals, and cumulative dosing were evaluated. All adverse events reported in each of the 3 trials, including available narratives, were assessed. The cut-off dates for data presented were for HAVEN 1 (primary analysis) September 2017; HAVEN 2 (interim analysis) October 2017; and HAVEN 4 (primary analysis) December 2017.[10]

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NovoSeven® RT **contains only rFVIIa[2]**

NovoSeven® RT is not made with any other coagulation factors, such as FIX or FIXa[2,6]

NovoSeven® RT[2]	FEIBA®[6]
Activated recombinant factor VII (rFVIIa)	Factors II, IX, and X mainly in nonactivated form as well as activated factor VII
	Factor VIII coagulant antigen (FVIII C:Ag) is present at a concentration of up to 1-6 units per mL of FEIBA
	Factors of the kallikrein-kinin system are present only in trace amounts

FEIBA contains activated and nonactivated coagulation factors, including FII, FVIII, FIX, and FX, which can accumulate with repeat dosing[6,12]

MASAC recommends patients with congenital hemophilia B with a history of inhibitors and anaphylaxis not be given FIX-containing products for acute bleeds.[13]

Important Safety Information

Warnings and Precautions

- Hypersensitivity reactions, including anaphylaxis, can occur with NovoSeven® RT. Patients with a known hypersensitivity to mouse, hamster, or bovine proteins may be at a higher risk of hypersensitivity reactions. Discontinue infusion and administer appropriate treatment when hypersensitivity reactions occur

Please see additional Important Safety Information throughout.
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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

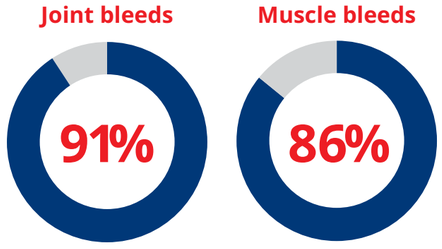
Effective bleed control in congenital hemophilia A or B with inhibitors

Proven trial results and real-world experience

93% efficacy seen in adept™2[14,a]

all bleed locations at 12 hours

- One of the largest clinical trials conducted in patients with CHwI
- Comparable efficacy seen in joint, target, mucocutaneous, muscle, and other bleeding episodes



Efficacy seen in Lusher et al[15,b]

- **98%** effective bleed control in patients ≤18 years, based on real-world experience[16]

[a]Data from an international, multicenter, randomized, double-blind, active-controlled, confirmatory phase 3 trial of patients with hemophilia A or B with inhibitors (n=69). Primarily carried out in the home setting, all bleeds were treated, and each bleeding episode was randomized (3:2) to infuse either 1 to 3 doses of vatreptacog alfa (340 bleeding episodes; 80 mcg/kg) or 1 to 3 doses of NovoSeven® RT (227 bleeding episodes; 90 mcg/kg) when bleed symptoms were recognized, preferably within 2 hours of onset. Primary efficacy endpoint indicated effective bleed control defined as no additional hemostatic reaction (other than the original medication) given within 12 hours after the initial dose.[14]
[b]Data from a randomized, double-blind, parallel-group, multicenter study of patients with hemophilia A and B with and without an inhibitor (n=84). Patients were given NovoSeven® 35 or 70 mcg/kg at dosing intervals of 2 to 3 hours. Efficacy reflects the number of patients reporting excellent, effective, or partially effective results. Response was rated as "excellent" if patient demonstrated definitive relief of pain/tenderness and/or if there was a measurable decrease in the size of the bleed (or arrest of bleeding) in 8 hours or less. An "effective" response was measured by any of these 3 events occurring from 8 to 14 hours; a "partially effective" response either occurred after 14 hours or indicated detectable relief of pain/tenderness or decrease in size of the hemorrhage or if the bleeding had slowed.[15]

Important Safety Information

Warnings and Precautions *(cont'd)*

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance

NovoSeven® RT **controls joint bleeds fast**

Hemostasis was achieved with a median of 2 doses[15]

Quick readministration

NovoSeven® RT can be readministered as quickly as every 2 hours compared with up to 12 hours for FEIBA[2,6]

Median 2 doses

A median of 2 doses helped control joint bleeds in as little as 5 hours[15,a]

Maximum activity

NovoSeven® RT achieved maximum activity within 5-10 minutes of infusion[3,c,d]

[c]Data from a randomized, double-blind trial of healthy subjects (N=22) who received 1 intravenous bolus injection each of NovoSeven® RT and NovoSeven®. Both bolus injections were 90 mcg/kg and occurred 2 to 3 weeks apart at consecutive visits. While the comparison is not shown for FVIIa, activity for NovoSeven® RT was the bioequivalent range of that for NovoSeven® during this period.[15]
[d]FVIIa activity IU/mL.[3]

Important Safety Information

Warnings and Precautions *(cont'd)*

- Patients with congenital hemophilia receiving concomitant treatment with aPCCs (activated prothrombin complex concentrates), older patients particularly with acquired hemophilia and receiving other hemostatic agents, and patients with a history of cardiac and vascular disease may have an increased risk of developing thrombotic events

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

Keep NovoSeven® RT on hand to **treat as early as possible**

Take control of acute bleeding episodes[a,b]

- 90 mcg/kg every 2 hours until hemostasis is achieved[2]
- For each patient, both the recommended dose of 90 mcg/kg and dosing interval can be adjusted based on the severity of bleeding[2,c]

NovoSeven® RT has **no maximum daily dose** restrictions when used within the approved regimen[2]

CHASE has CHAwI

[a]The appropriate duration of post-hemostatic dosing has not been studied.
[b]The minimum effective dose has not been determined.
[c]In patients with hemophilia A or B with inhibitors.

Important Safety Information

Warnings and Precautions *(cont'd)*

- Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity (FVII:C). If FVII:C fails to reach the expected level, or PT is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed

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The **speed to control** bleeds when they happen

Rapid infusion with less volume

- NovoSeven® RT has **16x less infusion volume** than FEIBA[2,6,c,d]

NovoSeven® RT
90 mcg/kg
8 mL

FEIBA
75 U/kg
132 mL

- NovoSeven® RT is up to **18x faster to infuse** than FEIBA[2,6,e]

NovoSeven® RT
90 mcg/kg
2-5 minutes

FEIBA
75 U/kg
37.5 minutes[d]

[d]Individual doses for a joint bleed are compared and based on an 88-kg (194 lb) person.
[e]Patients are cautioned that the maximum injection or infusion rate must not exceed 2 U/kg of body weight.

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

Early diagnosis and treatment are crucial in acquired hemophilia

Isolated, unexplained prolonged, aPTT in a patient with acute or recent-onset bleeding: a vital clue to acquired hemophilia[17,18]

Consult

When lab results show an unexplained, isolated, prolonged aPTT, consult a hematologist immediately [17,18]

Confirm

Delays in diagnosis and treatment put patients with acquired hemophilia at risk.[19,20] In fact, **AH is associated with death in 1 out of every 3 patients**[21]

Control the bleed with NovoSeven® RT

Model used for illustrative purposes only.

Important Safety Information

Warnings and Precautions *(cont'd)*

- Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis

Adverse Reactions

- The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® RT in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia

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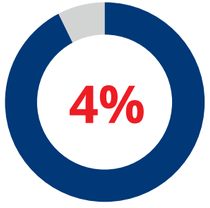
NovoSeven® RT: **The first and only bypassing agent FDA approved for AH**

Recombinant safety supported by clinical trials

Clinical trials[2]



Occurrence of thrombotic events

- Works at the site of vascular injury[2,22]
- Not made from human serum or human proteins[2]

Rapid access to treatment

- NovoSeven® RT can be infused in 2-5 minutes[2]
- Low-volume, flexible dosing for patients with AH[2]
  - 70-90 mcg/kg every 2-3 hours until hemostasis is achieved
- Room temperature stable up to 77˚F[2]

Using NovoSeven® RT first line improves its efficacy[23]

First-line treatment

Salvage therapy

- An international consensus recommends the use of NovoSeven® RT as first-line treatment for acquired hemophilia[17]

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

DALLAS has Glanzmann's thrombasthenia with refractoriness to platelet transfusions

Recognizing and properly treating Glanzmann's thrombasthenia

Diagnosing GT isn't always simple[24-28]

- Normal PT, aPTT, and platelet count do not indicate the absence of a bleeding disorder
- If a patient has mucocutaneous bleeds, consider screening for platelet defects
  - Automated platelet function tests (eg, PFA-100) screen for platelet dysfunction
  - Definitive diagnosis of GT requires more specific platelet function tests

Treating with platelets has potential complications

Patients who receive platelet transfusions are at risk of developing refractoriness to future transfusions and/or platelet antibodies.[27-31]

Refractoriness to platelet transfusions *with* antibodies to platelets

Refractoriness to platelet transfusions *without* antibodies to platelets

Treat with NovoSeven® RT[28,29]

Important Safety Information

Drug Interactions

- Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII

NovoSeven® RT: **The only recombinant bypassing agent for GT with refractoriness to platelets**

Proven effective in GT-related bleeds and surgery

All bleeding episodes[2,a]

All surgical procedures[2,b]

Recombinant safety supported by registry data

Thrombotic events in bleeding episodes[2]

- Not made from human serum or human proteins[2]

Rapid access to treatment

- NovoSeven® RT can be infused in 2-5 minutes[2]
- Low-volume, flexible dosing for patients with GT[2]
  - 90 mcg/kg every 2-6 hours in severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved
- Room temperature stable up to 77°F[2]

[a]Adjudicator-assessed effectiveness of treatment regimens in patients with GT (N=218) in all severe bleeding episodes and all surgical procedures (N=1073) based on review of Glanzmann's Thrombasthenia Registry (GTR) data unblinded to investigator-coded efficacy. Efficacy was evaluated on a 2-point scale (clinical assessment of success or failure of treatment regimen as a whole, blinded and unblinded to investigator-coded outcome) including 92 patients treated with NovoSeven® RT for 266 bleeding episodes and 77 patients treated for 160 surgical procedures.

[b]Data collected from the GTR and the Hemophilia & Thrombosis Research Society registry showed that 140 patients with GT received NovoSeven® RT for 518 bleeding episodes, surgeries, or traumatic injuries. In the GTR, 1 patient reported a serious adverse reaction (deep vein thrombosis) and 1 patient experienced 3 adverse reactions (nausea, headache, and dyspnea). In addition, 2 patients experienced fever and 1 patient experienced headache.

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

With congenital factor VII deficiency, **early treatment** is essential

Life-threatening bleeds present early in life[32,33]

- CNS and GI bleeds occur most frequently during the first 6 months of life
- 70% of patients under the age of 5 years started having joint bleeds

rFVIIa is recommended by MASAC to treat CFVIId[34]

Indications and Usage

NovoSeven® RT (coagulation Factor VIIa, recombinant) is a coagulation factor indicated for:

- Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and perioperative management in adults with acquired hemophilia

Important Safety Information

WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

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NovoSeven® RT: **The only factor product approved for CFVIId**

Effectively control bleeds

Trial patients[2]

Registry patients[2]

- NovoSeven® RT is 93% effective at stopping nonsurgical and surgical bleeds in people with CFVIId[a]

[a]Data from the published literature and internal sources for patients with FVII deficiency (N=70) treated with NovoSeven® for 124 bleeding episodes, surgeries, or prophylaxis regimens. Dosing ranged from 6 mcg/kg administered every 2 to 12 hours (except for prophylaxis [doses administered from 2 times per week up to 2 times per day]). Patients were treated with an average of 1 to 10 doses. Treatment was effective if bleeding stopped or the physician rated the treatment as effective.[2]

Rapid access to treatment

- NovoSeven® RT can be infused in 2-5 minutes[2]
- Low-volume, flexible dosing for patients with CFVIId[2]
  - 15-30 mcg/kg every 4-6 hours until hemostasis is achieved
- Room temperature stable up to 77˚F[2]

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Success speaks for itself

NovoSeven® RT: **Proven to effectively control bleeds in surgery across all 4 indications**

Proven efficacy during surgery

CHAwI and CHBwI[2,35,a]
Major and minor surgeries

AH[23]
Surgical bleeds

GT[2,b]
Surgical bleeds

CFVIId[2]
Surgical and nonsurgical bleeds

A proven safety profile for perioperative bleed management

- Low rate of thrombotic events in surgery based on clinical trials and registry data[2,c]
- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported

[a] In patients with hemophilia A or B with inhibitors. Actual length of postoperative period may vary. Data from a prospective, randomized trial comparing 35 mcg/kg with 90 mcg/kg rFVIIa, each given every 2 hours intraoperatively and in the first 48 hours, then every 2-6 hours throughout day 5. Beyond day 5, patients were treated with open-label 90 mcg/kg until discharge at the discretion of the investigator. A total of 29 patients underwent 11 major and 18 minor procedures.[35]

[b] Data collected from the GTR and the Hemophilia & Thrombosis Research Society registry showed that 140 patients with GT received NovoSeven® RT for 518 bleeding episodes, surgeries, or traumatic injuries. In the GTR, 1 patient reported a serious adverse reaction (deep vein thrombosis) and 1 patient experienced 3 adverse reactions (nausea, headache, and dyspnea). In addition, 2 patients experienced fever and 1 patient experienced headache.[2]

[c] 0.2% in patients with CHwI, 4% in patients with AH, <0.2% in patients with GT.[2]

Important Safety Information

Warnings and Precautions

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance

NovoSeven® RT: **Essential to control bleeds in surgery**

Flexible dosing before, during, and after surgery

- NovoSeven® RT can be used in both minor and major surgeries across 4 indications[2]
  - MASAC guidelines recommend administering rFVIIa to CHAwI patients taking emicizumab who will undergo major procedures to maintain adequate hemostasis at the discretion of the treating physician[9]
- NovoSeven® RT offers tailored perioperative dosing[2]

NovoSeven® RT is the only bypassing agent **approved for continuous infusion** in CHwI[2]

CHAwI and CHBwI	**Minor:** 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery. Followed by 90 mcg/kg every 2 hours after surgery for 48 hours, then every 2-6 hours until healing occurs. **Major:** 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery. Followed by 90 mcg/kg every 2 hours after surgery for 5 days, then every 4 hours or by continuous infusion at 50 mcg/kg/hr until healing occurs.
AH	70-90 mcg/kg immediately before surgery and every 2-3 hours for the duration of the surgery and until hemostasis is achieved.
GT	90 mcg/kg immediately before surgery and every 2 hours for the duration of the procedure, followed by 90 mcg/kg every 2-6 hours to prevent postoperative bleeding. Higher doses of 100-140 mcg/kg can be used for surgical patients who have clinical refractoriness with or without platelet-specific antibodies.
CVIId	15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of the surgery and until hemostasis is achieved. Adjust dose and frequency of injections to each individual patient. Doses as low as 10 mcg/kg of body weight can be effective.

- Can be re-dosed as quickly as every 2 hours during and after surgery[2]
- Can be infused in 2-5 minutes[2]

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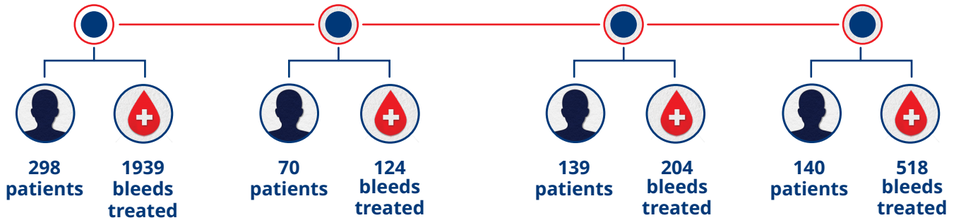
NovoSeven® RT experience **continues to grow**

CHAwI and CHBwI:
2 clinical studies[2]

CFVIId:
1 compassionate/emergency use program, published literature, 1 pharmacokinetics study, and 1 registry[2,36]

AH:
4 compassionate use programs, 1 registry, and published literature[2]

GT:
2 patient registries[2]



>30 years of research and long-term clinical experience[4]

647 patients and **2,785** episodes treated in registrational studies[2,36,a]

~400 successful surgeries and procedures[35,37-56,b]

[a]Includes bleeding episodes, major and minor surgical procedures, traumatic injuries, and prophylaxis regimens.
[b]Success was defined differently in each study.

Important Safety Information

Warnings and Precautions *(cont'd)*

- Patients with congenital hemophilia receiving concomitant treatment with aPCCs (activated prothrombin complex concentrates), older patients particularly with acquired hemophilia and receiving other hemostatic agents, and patients with a history of cardiac and vascular disease may have an increased risk of developing thrombotic events

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