



Thrombotic events with recombinant activated factor VII (rFVIIa) in approved indications are rare and associated with older age, cardiovascular disease, and concomitant use of activated prothrombin complex concentrates (aPCC)

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Purpose: Recombinant activated factor VII (rFVIIa; NovoSeven[®] RT; Novo Nordisk A/S, Bagsvaerd, Denmark) is approved in the United States for the treatment of bleeding and perioperative management in congenital hemophilia with inhibitors (CHwI), acquired hemophilia (AH), congenital factor VII (FVII) deficiency, and Glanzmann's thrombasthenia (GT) with refractoriness to platelets. The aim of the current analysis was to review clinical trials and registries pre- and post-licensure for each indication to establish the estimated rate of thrombosis and then to establish the association of all reported thrombotic events (TEs) with certain risk factors listed for many years in the prescribing information (PI).

Patients and methods: A retrospective safety assessment of both clinical trials and registries used to support licensure and postmarketing surveillance was performed. The rate of thrombosis was calculated in the 4 indicated disorders and an assessment of TE risk factors was conducted through a review of all narratives within those indications in the safety database.

Results: In clinical trials and registries used to support licensure and in postmarketing surveillance, the overall rate of thrombosis was 0.17% of 12,288 bleeding and surgical episodes. The specific risk by indication was 0.11% for CHwI, 0.82% for FVII deficiency, 0.19% for GT, and 1.77% for AH. The most common associated risk factor—"elderly" (29%), defined in the PI as age ≥ 65 years—was particularly prevalent in patients with AH. TE was also frequently reported with concomitant cardiac or vascular disease (18%) and use of activated prothrombin complex concentrates (18%).

Conclusion: Data show that the rate of TEs within the 4 licensed indications is low, as was originally described in the US PI from 1999 to 2009. It has remained stable over time during postapproval surveillance in multiple US and global registries with active surveillance for safety information across the 4 approved indications.

Keywords: postmarketing surveillance, acquired hemophilia, congenital hemophilia with inhibitors, congenital factor VII deficiency, Glanzmann's thrombasthenia

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Introduction

Recombinant activated factor VII (rFVIIa; NovoSeven[®] RT; Novo Nordisk A/S, Bagsvaerd, Denmark) is approved in the United States for the treatment of bleeding and perioperative management in congenital hemophilia with inhibitors (CHwI),

acquired hemophilia (AH), congenital factor VII (FVII) deficiency, and Glanzmann's thrombasthenia (GT) with refractoriness to platelets. The data supporting the development program for the current indications for rFVIIa since the first human dose in 1988 include an initial series of compassionate/emergency use studies, clinical trials (including pharmacokinetic, safety, and efficacy assessments), and national/international registries. Furthermore, safety data accumulated over the past 30 years encompass the literature (studies, case series, case reports) and spontaneous safety reporting.

Serious arterial and venous thrombotic events (TEs) have been reported in clinical trials and postmarketing surveillance; however, the incidence of this risk (rate of thrombosis) is considered to be low when rFVIIa is used within labeled indications.¹⁻⁴ TEs have been reported more frequently in AH than in other indications due to the older age of patients and the presence of comorbidities including cardiac and cardiovascular disease. The risks of TE associated with the use of rFVIIa in patients without bleeding disorders (outside of licensed indications) have been extensively studied.⁵⁻⁹

The aim of the current analysis was to review clinical trials and registries pre- and post-licensure for each of the 4 approved indications to establish the estimated rate of thrombosis and then to establish the association of reported TEs with certain risk factors listed for many years in the prescribing information (PI).

Materials and methods

A retrospective safety assessment of both clinical trials and registries used to support licensure and postmarketing surveillance was performed. The rate of thrombosis was calculated in the 4 indicated disorders: CHwI, AH, FVII deficiency, and GT.

Analysis considered all postmarketing TE case reports in the Novo Nordisk safety database through March 2017, including those from registries, spontaneous (unsolicited) reports, and the literature; isolated cases of catheter occlusion were not included. Event narratives were assessed to identify any of the risk factors listed in the PI and as a sensitivity analysis for additional risk factors associated with TE where there was a temporal relationship to rFVIIa use, which was defined as within 48 hrs, given the 2-3-hr half-life. Although manufacturer safety databases, including spontaneous reports, are not publicly available, TE data reported to the Federal Drug Administration (FDA)

are available through the FDA's Adverse Events Reporting System database.

Given the retrospective nature of these analyses, neither institutional review board nor ethics committee approval was required. All of the cited trials and registries were performed under the oversight of institutional ethics boards or national ethics committees.

Results

Rate of thrombosis

In clinical trials and registries used to support licensure and in postmarketing surveillance, the overall rate of thrombosis was 0.17% of 12,288 bleeding and surgical episodes (Table 1). Twenty-one TEs were identified (12 CHwI, 3 FVII deficiency, 1 GT, and 5 AH). The specific risk by indication was 0.11% for CHwI (11,121 episodes), 0.82% for FVII deficiency (367 episodes), 0.19% for GT (518 episodes), and 1.77% for AH (282 episodes). An additional Japanese postmarketing study in 132 patients with AH with 371 bleeding episodes reported 3 TEs and a thrombosis rate of 0.8%. This additional analysis reduced the calculated TE rate in AH from 1.77% (Table 1) to 1.2%.

Risk factors for thrombosis

Analysis of all postmarketing databases revealed 213 TEs (88 CHwI, 61 AH, 53 FVII deficiency, 11 GT; Table 2). The majority were reported spontaneously (unsolicited) to the manufacturer (141), with fewer reported in the literature (47) or solicited through safety reporting in registries or investigator-sponsored studies (25) (Table 2). Of 213 TE cases, temporal relationship was assessed as plausible in 188 (88.3%) cases, in which rFVIIa use was reported within 48 hrs prior to TE or the timing was unknown; timing was confirmed to be more than 48 hrs in 25 (11.7%) cases. Overall, the most common associated risk factor—"elderly," defined in the PI as age ≥ 65 years (28.6%)—was particularly prevalent in patients with AH and TE (67.2%; Table 3). Another common factor was concomitant use of activated prothrombin complex concentrates (aPCC), identified in 17.8% of all TEs and 34.1% of TEs in CHwI. Broadly defined cardiovascular disease (including cardiac arrhythmias) was noted in 17.8% of all TEs (36.1% AH, 15.1% FVII deficiency, 9.1% CHwI) and was much more common than specific note of atherosclerotic disease (1.9%). Other risk factors listed in the US PI (through October 2017) were uncommon, and in

Table I Thrombotic events in clinical studies

| | Number of patients with TE(s) | Number of bleeds and surgeries | Number of TEs | Thrombosis rate (%) |
|--|-------------------------------|--------------------------------|---------------|---------------------|
| Congenital hemophilia with inhibitors sBLA 103665/5442 approved January 15, 2010 | 7 | 4092 | 8 | 0.20 |
| Additional phase 1–4 studies | 4 | 7029 | 4 | 0.06 |
| NN7128-1907 (pioneer™ I) | 0 | 359 | 0 | 0.0 |
| NN1731-3562 (adept™2) | 1 | 227 | 1 | 0.4 |
| F7HRS-2117 (HTRS Registry, 2004–2011) | 0 | 2069 | 0 | 0.0 |
| F7HAEM-1965 (DOSE) | 0 | 158 | 0 | 0.0 |
| F7HAEM-3507 (ONE registry) | 0 | 496 | 0 | 0.0 |
| NN7025-3061 (SMART-7) | 0 | 592 | 0 | 0.0 |
| F7HAEM-3537 (UKHCDO Registry) | 0 | 1057 | 0 | 0.0 |
| F7HAEM-1947 (Japanese PMS) | 3 | 1718 | 3 | 0.2 |
| F7HAEM-1921 (WIRK registry) | 0 | 269 | 0 | 0.0 |
| F7HAEM-3850 | 0 | 84 | 0 | 0.0 |
| Total | 11 | 11,121 | 12 | 0.11 |
| Congenital FVII deficiency sBLA (CU/EU, HRS/HTRS, PK, literature) | 0 | 124 | 0 | 0.00 |
| CU/EU | 0 | 69 | 0 | 0.00 |
| HRS/HTRS (2000–2004) | 0 | 13 | 0 | 0.00 |
| Additional phase 4 study (STER) | 3 | 243 | 3 | 1.23 |
| Total | 3 | 367 | 3 | 0.82 |
| Glanzmann's thrombasthenia sBLA (GTR, HTRS) | 1 | 518 | 1 | 0.19 |
| GTR | 1 | 495 | 1 | 0.2 |
| HTRS (2004–2011) | 0 | 23 | 0 | 0.0 |
| Total | 1 | 518 | 1 | 0.19 |
| Acquired hemophilia sBLA (CU/EU, HRS/HTRS) | 3 | 113 | 5 | 4.4 |
| CU/EU | 2 | 100 | 4 | 4.0 |
| HRS/HTRS (2000–2004) | 1 | 13 | 1 | 7.7 |
| HTRS postmarketing surveillance (2004–2011) | 0 | 169 | 0 | 0.0 |
| Total | 3 | 282 | 5 | 1.77 |
| Total TEs across all indications | 18 | 12,288 | 21 | 0.17 |

Abbreviations: CU/EU, compassionate/emergency use program; DOSE, Dosing Observational Study in Hemophilia; FVII, factor VII; GTR, Glanzmann's Thrombasthenia Registry; HRS, Hemophilia Research Society; HTRS, Hemostasis and Thrombosis Research Society; ONE, Observational Registry of NovoSeven® Used as On-demand Treatment of Bleeds in Patients With Hemophilia A and B With Inhibitors; PMS, postmarketing survey; PK, pharmacokinetic study in congenital FVII deficiency; sBLA, supplemental Biologics License Application; STER, Seven Treatment Evaluation Registry; TE, thrombotic event; UKHCDO, United Kingdom Haemophilia Centre Doctors' Organization; WIRK, Observational Study on the Efficacy and Safety of NovoSeven® During "Real-life" Usage in Germany.

some cases, never identified in TE reports (eg, postoperative immobilization, sepsis, liver disease, disseminated intravascular coagulation, neonates, pregnancy, postpartum hemorrhage, crush injury).

Based on the 2–3-hr half-life of rFVIIa, the event was considered to have a temporal relationship to the

treatment if the time between the last dose of rFVIIa and the event onset was within 48 hrs or if the timing was unknown. Sensitivity analysis of TE cases with a possible temporal relationship (event onset within 48 hrs of last administration or unknown) demonstrated similar results (Table 3).

Table 2 Thrombotic events in safety reports

| Total TEs | CHwl | AH | C7D | GT | Total |
|--------------------------------|------|----|-----|----|-------|
| | 88 | 61 | 53 | 11 | 213 |
| Source of TEs | | | | | |
| Spontaneous reporting | 59 | 35 | 41 | 6 | 141 |
| Literature | 19 | 15 | 9 | 4 | 47 |
| Solicited | 10 | 11 | 3 | 1 | 25 |
| Temporal relationship | | | | | |
| Present (rFVIIa within 48 hrs) | 77 | 57 | 47 | 7 | 188 |
| Absent | 11 | 4 | 6 | 4 | 25 |

Abbreviations: AH, acquired hemophilia; C7D, congenital factor VII deficiency; CHwl, congenital hemophilia with inhibitors; GT, Glanzmann's thrombasthenia; rFVIIa, recombinant activated factor VII; TE, thrombotic event.

Table 3 Risk factors for thrombotic events

| Total TEs | CHwl | AH | C7D | GT | Total |
|---|-----------|-----------|-----------|----------|------------|
| | 88 | 61 | 53 | 11 | 213 |
| Risk factors | | | | | |
| Elderly (age ≥65 y) | 10.2% | 67.2% | 17.0% | 18.2% | 28.6% |
| Cardiac and/or vascular disease | | | | | |
| Cardiovascular disease | 9.1% | 36.1% | 15.1% | 0.0% | 17.8% |
| Atherosclerotic disease | 1.1% | 4.9% | 0.0% | 0.0% | 1.9% |
| Prothrombin complex conc. | | | | | |
| aPCC ^a | 34.1% | 13.1% | 0.0% | 0.0% | 17.8% |
| PCC | 2.3% | 0.0% | 1.9% | 0.0% | 1.4% |
| Septicemia/sepsis | 4.5% | 4.9% | 5.6% | 0.0% | 4.7% |
| Liver disease | 8.0% | 3.3% | 3.8% | 9.1% | 5.6% |
| Immobilization | 4.5% | 1.6% | 3.8% | 9.1% | 3.8% |
| DIC | 1.1% | 1.6% | 0.0% | 0.0% | 0.9% |
| Neonates | 0.0% | 0.0% | 1.9% | 0.0% | 0.5% |
| Pregnancy/PPH | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Crush injury | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| TEs with a temporal relationship to rFVIIa | 77 | 57 | 47 | 7 | 188 |
| Risk factors | | | | | |
| Elderly (age ≥65 y) | 10.4% | 66.6% | 17.0% | 14.3% | 29.3% |
| Cardiac and/or vascular disease | | | | | |
| Cardiovascular disease | 10.4% | 35.1% | 17.0% | 0.0% | 19.1% |
| Atherosclerotic disease | 1.3% | 5.3% | 0.0% | 0.0% | 2.1% |
| Prothrombin complex conc. | | | | | |
| aPCC ^a | 33.8% | 14.0% | 0.0% | 0.0% | 18.1% |
| PCC | 1.3% | 0.0% | 2.1% | 0.0% | 1.1% |
| Septicemia/sepsis | 5.2% | 3.5% | 6.4% | 0.0% | 4.8% |
| Liver disease | 9.1% | 3.5% | 4.3% | 0.0% | 5.8% |
| Immobilization | 5.2% | 0.0% | 2.1% | 0.0% | 2.7% |
| DIC | 0.0% | 1.7% | 0.0% | 0.0% | 0.5% |
| Neonates | 0.0% | 0.0% | 2.1% | 0.0% | 0.5% |
| Pregnancy/PPH | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Crush injury | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |

Note: ^aaPCC with or without factor VIII or antifibrinolytics.

Abbreviations: AH, acquired hemophilia; aPCC, activated prothrombin complex concentrates; C7D, congenital factor VII deficiency; CHwl, congenital hemophilia with inhibitors; DIC, disseminated intravascular coagulation; GT, Glanzmann's thrombasthenia; PCC, prothrombin complex concentrates; PPH, postpartum hemorrhage; rFVIIa, recombinant activated factor VII; TE, thrombotic event.

Discussion

Safety data collected over the past 30 years have demonstrated a good safety profile for rFVIIa within the 4 indicated disorders. In the current retrospective safety analysis of both extensive clinical trials and registries used to support licensure and postmarketing surveillance, 21 TEs were identified in 18 patients treated for 12,288 bleeding and surgical episodes, generating a TE rate of 0.17%. Previous retrospective studies of rFVIIa postmarketing surveillance identified varying rates of TEs due to differences in the sources of data (eg, registries, clinical trials, literature reviews, spontaneous [unsolicited] reports) and time frames of each analysis, but overall, the incidence of TEs with rFVIIa use within the 4 licensed indications was very low.

Rates of TEs are easily calculated from registries in which the number of TEs and the total number of bleeding episodes are collected, and in which safety data are required to be reported (eg, mandatory field affirming presence/absence of adverse reactions). For example, an analysis of Hemostasis and Thrombosis Research Society registry data from 2004 to 2008 found 0 TEs in 2041 rFVIIa-treated bleeding events, yielding a rate of 0.00%.¹⁰

Other postmarketing surveillance analyses that included spontaneous and clinical trial reports and registry data found 25 TEs between 1996 and 2003¹ and 30 TEs between 2003 and 2006.⁷ The approaches used in these analyses allow for the determination of the number of TEs. Using an estimation of the number of standard (90 mcg/kg) rFVIIa doses given during that time frame, an approximation of the rate of TEs can be calculated. An additional review of safety data from 1996 to 2013 found 195 TEs among the estimated 4 million rFVIIa doses.³ The most recent cumulative review identified 217 TEs between 1996 and 2016, a period covered by an estimated 5.4 million standard doses.⁴

Spontaneous reports to manufacturers can be subject to poor-quality data lacking detail, limiting their usefulness in safety analyses. In addition, as these reports are unsolicited, it is possible that the number of TEs relayed through spontaneous reports is underestimated; however, this underestimation is likely balanced by an under-reporting of rFVIIa usage. Clinical trials are a more reliable source of data because they have more stringent safety reporting (eg, mandated affirmations of presence/absence of adverse events for each episode) and follow-up compared with spontaneous reports. However, there are limitations to using only clinical trials for safety analyses. For example, many trials have exclusion criteria that limit the population of eligible patients and therefore do

not reflect the real-world population; compassionate/emergency use studies and registries are more inclusive of real-world populations and constitute the majority of rFVIIa clinical data. Therefore, the 21 TEs within the 12,288 bleeds and surgeries accumulated in compassionate/emergency use studies, clinical trials, and real-world registries performed over 30 years throughout the world are a better reflection of the true incidence of adverse events in a controlled setting in terms of mandatory safety reporting. In the current analysis, the addition of spontaneous reports of TEs with a varied patient population is best used to help identify safety signals such as the risk factors for TEs.

This study highlights the importance of understanding the risk factors for thrombosis in patients with hemophilia. For more than a decade, risk factors typically associated with thrombosis in patients without an underlying bleeding disorder were included in the PI as warnings, perhaps due in part to previous clinical trials with rFVIIa outside the 4 currently indicated disorders. However, the present analysis suggests that older age, cardiac and cardiovascular disease (beyond atherosclerosis only), and concomitant use of aPCC are the most common associated risk factors for thrombosis among patients with hemophilia. The validity of the current analytical approach to risk factor identification is supported by the inclusion of this new information in the 2018 PI update to the warnings around TE risk.

As new generations of treatments, such as non-factor products and gene therapy, become available and are combined with factor products and bypassing agents for breakthrough bleeds and surgeries, the risk of TE must be considered. Prescribers will require detailed information about factors that may predict risk. It is essential to balance the degree of hemostasis with the desire to avoid any bleeding and possible product/molecule-specific interactions with acute hemostatic treatment. Importantly, thus far, no safety concerns with concomitant use of rFVIIa and emicizumab have been identified.^{4,11,12}

Conclusion

These data demonstrate that the rate of TEs within the 4 licensed indications is low (0.17%), as was originally described in the US PI from 1999 to 2009. It has remained stable over time during postapproval surveillance in multiple US and global registries with active surveillance for safety information across the 4 approved indications. Based on an assessment of postmarketing safety reports, patients with CHwI receiving concomitant treatment with

aPCC, older patients, particularly those with AH who are receiving other hemostatic agents, and patients with a history of cardiac and cardiovascular disease may have an increased risk of developing TEs.

Abbreviations

AH, acquired hemophilia; aPCC, activated prothrombin complex concentrates; CHwI, congenital hemophilia with inhibitors; FVII, factor VII; GT, Glanzmann's thrombasthenia; PI, prescribing information; rFVIIa, recombinant activated factor VII; TEs, thrombotic events.

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Disclosure

MR has served as an advisory board member for Novo Nordisk, HEMA Biologics, Spark Therapeutics and Takeda. MR reports personal fees from Novo Nordisk and Spark Therapeutics, outside the submitted work. SEC has consulted for Pfizer, Shire, Bayer, CSL-Behring, Genentech, Novo Nordisk, and Octapharma. She has received grant and honorarium from Pfizer and Octapharma, outside the submitted work. LB has served as an advisory board member for Novo Nordisk, Baxalta, CSL, and Octapharma, outside the submitted work. DLC is an employee of Novo Nordisk Inc. The authors report no other conflicts of interest in this work.

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