as are other data on inhibitor rates from other prospective or retrospective studies. The continued accumulation of data on inhibitor development will help us to better understand this clinical challenge and hopefully lead to improved care for our patients, which is the ultimate goal of all medical research.

DISCLOSURES

R.J. Liesner has received grants/research support from Octapharma, Bayer, Baxalta, Novo Nordisk and Roche, has acted as a consultant for Bayer and Baxalta and has participated in speaker bureaus for Octapharma, SOBI and Novo Nordisk. Medical writing support was provided by nspm ltd, Meggen, Switzerland, with financial support from Octapharma.

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Accepted: 18 May 2018
DOI: 10.1111/hae.13547

Recombinant activated factor VII in approved indications: Update on safety

Recombinant activated factor VII (rFVIIa; eptacog alfa activated, NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) is a bypassing agent indicated for the treatment of bleeding episodes and the prevention of bleeding during surgery or invasive procedures, in patients with congenital haemophilia A and haemophilia B (who have inhibitors to coagulation factor [F] VIII or FIX, respectively), in patients with acquired haemophilia or congenital FVII deficiency and also in patients with Glanzmann thrombasthenia with refractoriness and/or platelet-specific antibodies (or where platelets are not readily available).[1-4]

Due to their mode of action, all procoagulant agents have the potential to cause thrombotic complications.[5] However, the incidence of thrombotic events (TEs) that has been reported for rFVIIa was low.[6] Recombinant FVIIa has been used successfully in clinical practice for more than two decades following its approval in 1995,[2] showing a consistently favourable safety profile in all licensed indications. The last review on the safety of rFVIIa covered the period from the approval of rFVIIa in 1996 through to 31 December 2013.[6] Since that time, one million further standard 90 μg/kg doses of rFVIIa have been administered. The aim of this report was to provide an updated safety evaluation of rFVIIa based on available data from clinical trials, post-marketing surveillance and observational, non-interventional studies, concentrating on the reporting of TEs in all approved indications.

The cumulative review period was from 1 January 1996 through to 31 December 2016. Data were included from solicited and spontaneously reported cases from the Novo Nordisk safety database and published literature, and solicited reports gathered from 17 observational, non-interventional clinical trials (Table S1a and b). This cumulative safety review also included data obtained from clinical trials reported in prior reviews; no new clinical trials have been conducted since the last safety update published in 2015.[6] The rFVIIa total exposure was calculated for all four approved indications and was based on the number of standard doses (defined as 90 μg/kg calculated based on an average individual weighing 40 kg, as per the first rFVIIa safety review conducted by Abshire and Kenet[7]) sold globally since the launch of the product. Safety data were evaluated and TEs were those reported from all licensed indications (congenital haemophilia with inhibitors, acquired haemophilia, Glanzmann thrombasthenia, congenital FVII deficiency). TEs were classified as arterial, venous or mixed, according to the Standard Medical Query (SMQ) "Embolic and thrombotic events" from the Medical Dictionary for Regulatory Activities (MedDRA).

Over the cumulative review period, the estimated overall exposure to rFVIIa across all approved indications was approximately 5.4 million standard doses. Tables 1 and 2 report the number of cases of TEs and their outcomes during the reporting period for all approved indications. Overall, 217 patients experienced one or more TE (Table 1), 95 of whom (44%) had recovered, or were recovering, at the time of reporting (Table 2). For 42 of the 217 cases (19%), TEs were fatal. No cases of thrombotic microangiopathy have been reported.

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TABLE 1 Overall distribution of thrombotic events (TEs) in approved indications reported from postmarketing sources, observational studies, registries, spontaneous reporting and literature cases

	Total number of cases (patients) with one or more TEs	Number of arterial TEs	Number of venous TEs	Number of mixed TEs	Total number of TEs
Congenital haemophilia with inhibitors	91	17	46	42	105
Acquired haemophilia	66	26	17	29	72
Congenital factor VII deficiency	49	10	30	17	57
Glanzmann thrombasthenia	11	1	9	5	15
Total	217	54	102	93	249

Cumulative data up to 31 December 2016.

TABLE 2 Outcomes of thrombotic events (TEs) in approved indications reported for recombinant activated factor VII from postmarketing sources, observational studies, registries, spontaneous reporting and literature cases

		Number of cases reported with the following outcomes:				
	Total number of cases (patients) with one or more TEs	Fatal	Recovered/recovering	Recovered with sequelae	Not recovered	Unknown
Congenital haemophilia with inhibitors	91	11	49	2	14	15
Acquired haemophilia	66	26	20	5	4	11
Congenital factor VII deficiency	49	3	22	6	5	13
Glanzmann thrombasthenia	11	2	4	1	3	1
Total	217	42	95	14	26	40

Cumulative data up to 31 December 2016.

Of 105 TEs in 91 patients with congenital haemophilia with inhibitors, 44% of these TEs were venous and 40% were mixed (Table 1). The majority of patients (54%) with this indication experiencing at least one TE had recovered, or were recovering, at the time of reporting. The TE was reported to be fatal for 12% of patients (Table 2). For acquired haemophilia, a total of 72 TEs were reported in 66 patients, with 40% of the TEs being mixed and 36% being arterial (Table 1); 30% of the patients with one or more TE had recovered, or were recovering, at the time of reporting (Table 2). A fatal outcome occurred in 39% of the patients reporting one or more TE. A total of 57 TEs were reported in 49 patients with congenital FVII deficiency. Of these, the majority were venous (53%) (Table 1). Of the 49 patients, 22 (45%) had recovered, or were recovering, at the time of reporting. Only 6% of cases were reported to be fatal (Table 2). Of a total of 15 TEs reported in 11 patients with Glanzmann thrombasthenia, the majority were venous (60%) (Table 1). Thirty-six per cent of patients had recovered, or were recovering, at the time of reporting, with 18% of cases being reported to be fatal (Table 2).

Effectiveness data of rFVIIa for the treatment of bleeds and surgeries available from the postmarketing surveillance studies, observational/non-interventional studies and registries from which solicited reports on safety events were obtained (1 January 1996 to 31 December 2016) are provided in Table S1a and b. Although effectiveness was measured and defined differently across studies, the data presented show the consistent effectiveness of rFVIIa over the 20 years of its postmarketing use. When used alone for the treatment of acute bleeds, rFVIIa was effective or partially effective in stopping between 86.3% and 94.6% of bleeds in congenital haemophilia with inhibitors, 88.9% of bleeds in acquired haemophilia (Table S1a), provided "excellent" or "effective" outcomes between 82% and 95.4% of bleeds in patients with congenital FVII deficiency, and was rated as effective in 91% of bleeds in Glanzmann thrombasthenia (Table S1a). For surgery and invasive procedures, rFVIIa stopped bleeding in 91% of procedures performed in congenital haemophilia with inhibitors, was rated as excellent/good in 77.3% and fair/partially effective in 9.1% of bleeds in patients with acquired haemophilia, and prevented bleeding in 100% of surgical or invasive procedures in individuals with congenital FVII deficiency or Glanzmann thrombasthenia (Table S1b).

This updated safety report now provides cumulative safety data from 20 years of rFVIIa use in its four approved indications involving over 5.4 million doses of this bypassing agent. Recombinant FVIIa continues to maintain its favourable safety profile, with no new or unexpected safety concerns occurring since the last review of this agent's safety.[6] Overall, the number of reported TEs was low across

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all the approved indications compared with the estimated number of administered doses of rFVIIa. A theoretical basis for this outcome lies with the localized mechanism of action of rFVIIa, which causes limited systemic activation of coagulation and therefore does not increase the risk of thrombosis.[6, 8] Nevertheless, it is important to closely monitor all patients treated with rFVIIa for signs and symptoms of TEs, especially if they are elderly or if they have concomitant conditions and/or predisposing risk factors for thrombosis.

With the emergence of new prophylactic therapies for haemophilia, how best to treat patients who experience acute bleeding episodes when treated with these new therapies is an area of interest. In patients with congenital haemophilia with high inhibitor levels, in addition to rFVIIa, plasma-derived activated prothrombin complex concentrate (pd-aPCC; FEIBA®, Baxalta US Inc, Westlake Village, CA, USA) is also indicated for the on-demand treatment of bleeds.[9] Both bypassing agents have been used to treat bleeding episodes in a recent trial of emicizumab, a bispecific antibody to FIX and FX designed to replace the cofactor function of FVIII, that explored the efficacy of the prophylactic use of emicizumab in haemophilia A patients with inhibitors.[10] While no cases of thrombotic microangiopathy or TEs were linked to the use of rFVIIa when used in conjunction with emicizumab, it should be remembered that these data are based on the treatment of small numbers of patients and bleeding episodes and that further surveillance is required. Careful observation of patients when receiving concomitant prophylaxis with new haemophilia and bypassing agents is warranted.

The data summarized above provide a baseline for the incidence of TEs with rFVIIa alone, which is important in an era when the safety of rFVIIa use in combination with novel treatments will require careful evaluation. A limitation of this analysis is that the spontaneous reporting of TEs from postmarketing sources may be biased, with the possibility that some events may have been under- or over-reported. Moreover, some reported TEs may reflect the disease state and/or clinical setting and may not be specific to treatment. Nevertheless, the outcomes of such evaluation will provide evidence-based recommendations for the use of rFVIIa in combination with novel agents.

In conclusion, rFVIIa has a continuing favourable safety profile in its four approved indications, with a low overall number of TEs reported together with the large number of rFVIIa doses administered over the last 20 years.

DISCLOSURES

S Benchikh el Fegoun and A Rojas-Rios assessed the Novo Nordisk safety database and collated the safety data. The manuscript was written and edited by all authors, and all authors reviewed and approved the final submitted version. EJ Neufeld and C Négrier have served as consultants and as advisory board members for Novo Nordisk. S Benchikh el Fegoun is an employee of Novo Nordisk Health Care AG, Switzerland, and a Novo Nordisk shareholder. DL Cooper is an employee of Novo Nordisk Inc., USA. S Seremetis is an employee of Novo Nordisk Inc., USA, and a Novo Nordisk shareholder. A Rojas-Rios is an employee of Novo Nordisk A/S, Denmark, and a Novo Nordisk shareholder. Editorial and writing assistance was provided by Sharon Eastwood, DPhil, of Fishawack Communications Ltd, and was funded by Novo Nordisk.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

1. **In conclusion, rFVIIa has a continuing favourable safety profile in its four approved indications, ...**
Anchor Name: Safety profile *[VJYA (Vijay A)]*