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Safety update on the use of recombinant activated factor VII in approved indications

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ABSTRACT

This updated safety review summarises the large body of safety data available on the use of recombinant activated factor VII (rFVIIa) in approved indications: haemophilia with inhibitors, congenital factor VII (FVII) deficiency, acquired haemophilia and Glanzmann's thrombasthenia. Accumulated data up to 31 December 2013 from clinical trials as well as post-marketing data (registries, literature reports and spontaneous reports) were included. Overall, rFVIIa has shown a consistently favourable safety profile, with no unexpected safety concerns, in all approved indications. No confirmed cases of neutralising antibodies against rFVIIa have been reported in patients with congenital haemophilia, acquired haemophilia or Glanzmann's thrombasthenia. The favourable safety profile of rFVIIa can be attributed to the recombinant nature of rFVIIa and its localised mechanism of action at the site of vascular injury. Recombinant FVIIa activates factor X directly on the surface of activated platelets, which are present only at the site of injury, meaning that systemic activation of coagulation is avoided and the risk of thrombotic events (TEs) thus reduced. Nonetheless, close monitoring for signs and symptoms of TE is warranted in all patients treated with any pro-haemostatic agent, including rFVIIa, especially the elderly and any other patients with concomitant conditions and/or predisposing risk factors to thrombosis.

1. Introduction

Recombinant activated factor VII (rFVIIa, eptacog alfa activated, NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) is a bypassing agent originally developed for the management of bleeding in haemophilia A and B patients with inhibitors to factor (F) VIII or FIX, respectively [1]. First approved for use in Europe in 1996, rFVIIa is currently licensed for the treatment of bleeding episodes and for the prevention of bleeding during surgery or invasive procedures in patients with congenital haemophilia A or B and inhibitors (>5 Bethesda units [BU]), and in those expected to have a high anamnestic response to FVIII or FIX concentrates. In Europe and some other regions of the world, rFVIIa is also approved for the treatment of bleeding episodes and prevention of bleeding during surgery or invasive procedures in patients with acquired haemophilia, congenital FVII deficiency, and Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusion (and in some countries where platelets are not available) [1–3].

The original formulation of rFVIIa, which required storage at 2–8°C, has now been replaced by a room temperature stable formulation, which has been developed to be stored at temperatures up to 25°C, and remains stable for 6 hours at 25°C and for 24 hours at 5°C, once reconstituted [4]. Bioequivalence between the original and new room temperature stable formulation has been demonstrated. Furthermore, as the drug itself remains the same in the new formulation, the activity established for the original formulation of rFVIIa is maintained [5].

All procoagulant agents have the potential to contribute towards the development of thrombosis and thromboembolism [6]. However, the incidence of thrombotic events (TEs) associated with both standard (90 μg/kg) and higher (270 μg/kg) doses of rFVIIa within approved indications has remained low [1,7–9]. The consistently favourable safety profile of rFVIIa may be attributable to its localised mechanism of action at the site of vascular injury. Here, where tissue factor (TF) is expressed and activated platelets are found [10], rFVIIa binds to TF and this initiates coagulation, which leads to the generation of small amounts of thrombin [11]. This thrombin then goes on to activate platelets. When administered in pharmacological doses, rFVIIa activates FX on the surface of activated platelets [12,13]; FXa then forms a complex with FVa to generate a large thrombin

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'burst' [14]. The thrombin burst produces a stable haemostatic plug at the site of vascular injury [12], resulting in bleeding control. This localised action of rFVIIa is therefore thought to provide a local pharmacological effect without general activation of coagulation [15]: *in vitro* studies have demonstrated a lack of free thrombin generation following the addition of rFVIIa to FVIII- and FIX-deficient plasma, suggesting that rFVIIa does not induce a hypercoagulable state in blood from patients with haemophilia [16].

The last safety update on rFVIIa (based on labelled indications at the time) was published in 2008 and covered the period from May 2003 to December 2006 [8]. The reporting rate of serious TEs at that time was much less than 1%, based on a Novo Nordisk internal database and projected sales in congenital and acquired haemophilia. However, as only data accrued from congenital haemophilia with inhibitors and acquired haemophilia were assessed [8], the aim of the current review is to provide an update on rFVIIa safety, using available data from clinical trials and post-marketing use (e.g. registries, observational studies, literature reports and spontaneous reports) in all licensed indications.

2. Methods

2.1. Data sources

The cumulative review period included data up to 31 December 2013. These data incorporated post-marketing data from solicited and spontaneously reported cases, including case reports from the literature. Solicited reports on adverse events (AEs) were gathered from 16 post-marketing studies, observational studies and registries (listed in Table 1), covering all approved indications. The solicited reports included in this analysis are those that were captured in the Novo Nordisk safety database; some of these reports were limited to serious adverse reactions only. Previous reviews have reported summarised safety data collected from clinical trials conducted before 2006 in congenital haemophilia with inhibitors and acquired haemophilia only [7,8]; this review includes detailed information from four subsequent clinical trials conducted in patients with congenital haemophilia and inhibitors between November 2007 and August 2012 [17–20], including the adept™2 trial [18]. Safety information from the pre-licensure compassionate use programme was also reviewed to capture immunogenicity events in acquired haemophilia as well as potential TEs and immunogenicity events in Glanzmann's thrombasthenia and congenital FVII deficiency.

2.2. Safety data

The focus of this safety review is TEs and immunogenicity in patients receiving rFVIIa for the treatment of congenital haemophilia with inhibitors, acquired haemophilia, congenital FVII deficiency or Glanzmann's thrombasthenia. It is important to note that the cases reported and presented may not necessarily be related to rFVIIa treatment, but may be due to underlying diseases or comorbidities.

2.2.1. Thrombotic events

TEs for this report were defined as either arterial, venous or mixed, according to the Medical Dictionary of Regulatory Activities (MedDRA). The rationale for this division lies in the differing pathophysiologies traditionally ascribed to clots in the arterial and venous systems [21–23]. While both types of clots are composed of platelets and fibrin [22], arterial thrombi typically occur at sites of arterial plaque rupture where shear rates are high, resulting in platelet-rich 'white thrombi' [21,22]. The primary risk factor for arterial thrombosis is atherosclerosis [22–24]. As the arterial system is a high-flow, high-pressure environment, arterial thrombi are prone to embolisation and can therefore cause ischaemic injuries, especially in tissues with a terminal vascular bed [23]. Arterial TEs carry high morbidity and mortality risks, and the most common types are myocardial infarctions and ischaemic cerebrovascular accidents (CVA) [23,25].

In contrast, venous thrombi tend to develop at sites where the vein wall is undamaged and where blood flow and shear stress are low, producing 'red thrombi' that are rich in red blood cells [21–23]. The pathogenic mechanisms of venous thrombosis are only partially understood, but a combination of stasis and hypercoagulability is known to be crucial [23]. Primary risk factors include trauma and major orthopaedic or oncological surgery [23], but venous thrombosis can occur spontaneously in individuals with genetic abnormalities associated with hypercoagulability [26,27]. Examples of venous TEs include superficial vein thrombosis, deep vein thrombosis (DVT) and pulmonary embolism. If DVT occurs in the deep leg veins, there is a risk of clot dislodgement and embolisation to the pulmonary circulation, resulting in pulmonary embolism that may be lethal [23,28].

In this review, 'mixed TEs' are those events that may be classified as being either arterial or venous in nature (e.g., disseminated intravascular coagulation [DIC], which is associated with clot formation in both arteries and veins). If the source data did not contain enough information to classify a TE as arterial or venous, it was categorised as 'mixed'.

2.2.2. Immunogenicity

Where possible, all occurrences of antibody development were classified as either binding-only or neutralising antibodies.

3. Results

3.1. Overall exposure and adverse events: all indications

Overall, the estimated total number of rFVIIa standard doses (90 μg/kg) used across all approved indications between 1996 and 2013 is 4 million. The estimation of standard doses was calculated based for an individual weighing 40 kg [7,8].

Fifteen percent of the total AEs were TEs reported from post-marketing sources (Table 2). Overall, the majority of patients (47%) with TEs recovered, or were recovering, at the time of reporting, while 18% of the patients with TEs died (Table 3).

Clinical trials or studies on rFVIIa have been conducted only in patients with congenital haemophilia and inhibitors, acquired haemophilia and congenital FVII deficiency. A total of one TE has been reported in these indications (patients with congenital haemophilia and inhibitors, no clinical trials performed in other indications) over the current review period (January 2007 to December 2013) and eight in the previous safety updates [7,8].

3.2. Congenital haemophilia with inhibitors

3.2.1. Thrombotic events

A summary of TEs (and associated outcomes) reported with rFVIIa use in congenital haemophilia with inhibitors throughout the review period is provided in Tables 2, 3 and 4.

Thirteen percent of the AEs reported from post-marketing sources for patients with congenital haemophilia treated with rFVIIa were TEs. The majority (44%) were venous TEs (Table 2), and most patients (60.3%) had recovered without sequelae, or were recovering, at the time of data collection; 12% of the patients died (Table 3).

Since 2006, one TE was reported across the clinical trials included in this analysis (Table 4). This TE was a thrombus of

Table 1
Post-marketing surveillance studies, observational/non-interventional studies and registries from which solicited reports on safety events were obtained (1 January 1996 to 31 December 2013)

Novo Nordisk study identification number (publications, where available)[a]	Study type	Description	Patients	Date
F7HRS-2117 (HRS/HTRS) (Al-Mondhiry et al., 2012 [73]; Ma et al., 2011, 2012 [74,75]; Parameswaran et al., 2005 [76])	Registry (HRS/HTRS), Novo Nordisk sponsored, post-approval commitment	Treatment with rFVIIa for bleeds and surgery	CHwI, AH, FVII CD, GT	October 1999–December 2003
		Treatment with rFVIIa for bleeds and surgery	CHwI, AH, FVII CD, GT	January 2004–December 2008
		Any treatment with rFVIIa	AH	November 2007–November 2011
F7-1947	Observational, post-approval commitment	Phase IV, treatment of bleeds (Japan)	CHwI, AH	March 1999–March 2010
F7-1948 (Takedani et al., 2014 [77])	Observational, post-approval commitment	Phase IV, surgery (Japan)	CHwI, AH	March 1999–March 2010
F7-1949	Observational, post-approval commitment	Phase IV, immunogenicity (Japan)	CHwI, AH	March 1999–March 2010
F7HAEM-3578 F7CONGDEF (Mariani et al., 2011, 2012 [42,66])	Registry (STER), post-approval commitment	Phase IV, rFVIIa treatment of bleeds and surgery	FVII CD	March 2004–January 2012
F7HAEM-3578 F7CONGDEF-PPX (Napolitano et al., 2013 [67])	Registry (STER)	Phase IV, prophylactic treatment	FVII CD	March 2004–January 2012
F7HAEM-3521 F7GLANZ (Di Minno et al., 2013 [63]; Poon et al., 2013 [68])	Registry (GTR), post-approval commitment	Phase IV, all treatment modalities, bleeds and surgery	GT	December 2004–December 2011
F7HAEM-3537 (Hay et al., 2013 [78])	Observational (UKHCDO), post-approval commitment	Phase IV, high doses of rFVIIa for the treatment of bleeds	CHwI	January 2008–June 2011
F7HAEM-3507 (Chambost et al., 2013 [62])	Observational (ONE), post-approval commitment	Phase IV, real-life use of rFVIIa (1–3 × 90 μg/kg and 1 × 270 μg/kg) for the treatment of bleeds	CHwI	March 2008–July 2010
F7HAEM-1921 (Birschmann et al., 2013 [61])	Observational (WIRK)	Phase IV, rFVIIa efficacy in routine practice, treatment of bleeds and surgery	CHwI, AH, FVII CD, GT	March 2008–December 2010
F7HAEM-1965 (Young et al., 2012 [79])	Observational (DOSE)	Phase IV, real-life use of rFVIIa in the treatment of bleeds	CHwI	June 2008–July 2009
F7HAEM-3695 (Young et al., 2012 [80])	Observational (PRO-PACT)	Phase IV, rFVIIa in prophylactic use	CHwI	August 2008–June 2010
F7HAEM-3850 (Belhani et al., 2013 [81])	Observational (BAAGI)	Phase IV, real-life use of rFVIIa in the home treatment of joint bleeds	CHwI	October 2010–April 2012
F7HAEM-3856	Observational (AQUI-7)	Phase IV, use of rFVIIa in the treatment of bleeds and surgery (France)	AH	December 2010–October 2013
F7HAEM-3862	Observational, post-approval commitment	Phase IV, use of rFVIIa (Japan)	FVII CD	March 2011–September 2014
F7HAEM-3864 (Shapiro et al., 2014 [82])	Observational	Phase IV, retrospective follow-up assessment of F7HAEM/USA/3/USA and F7HAEM/USA/4/USA	CHwI, AH	April 2011–January 2012
NN7025-3601 (Kavakli et al., 2014 [65])	Observational (SMART-7) post-approval commitment	Phase IV, safety/immunogenicity of rFVIIa room temperature stable formulation, treatment of bleeds and surgery	CHwI	November 2012 (ongoing)

HRS, Hemophilia Research Society; HTRS, Hemostasis and Thrombosis Research Society; rFVIIa, recombinant activated factor VII; CHwI, congenital haemophilia with inhibitors; AH, acquired haemophilia; FVII CD, congenital factor VII deficiency; GT, Glanzmann's thrombasthenia; STER, Seven Treatment Evaluation Registry; GTR, Glanzmann's Thrombasthenia Registry; UKHCDO, United Kingdom Haemophilia Centre Doctors' Organisation; DOSE, Dosing Observational Study in Haemophilia.

[a] Data from some of the post-marketing surveillance studies, observational studies and registries from which solicited reports on safety events were obtained have not been published.

Table 2
Overall distribution of thrombotic events (TEs) in approved indications reported for recombinant activated factor VII from post-marketing sources, observational studies, registries, spontaneous reporting, and literature cases. Cumulative data up to 31 December 2013

	Total no. of cases (patients) with one or more TEs	No. of arterial TEs	No. of venous TEs	No. of mixed TEs	Total no. of TEs
Acquired haemophilia	**50**	21	12	21	**54**
Congenital factor VII deficiency	**38**	7	24	14	**45**
Glanzmann's thrombasthenia	**8**	0	7	5	**12**
Congenital haemophilia	**73**	13	37	34	**84**
Total	**169**	**41**	**80**	**74**	**195**

Table 3
Outcomes of thrombotic events (TEs) in approved indications reported for recombinant activated factor VII from post-marketing sources, observational studies, registries, spontaneous reporting, and literature cases. Cumulative data up to 31 December 2013

		Number of cases reported with the following outcomes:				
	Total no. of cases (patients) with one or more TEs	Fatal	Recovered/ recovering	Recovered with sequelae	Not recovered	Unknown
Acquired haemophilia	**50**	19	14	4	4	9
Congenital factor VII deficiency	**38**	0	20	5	5	8
Glanzmann's thrombasthenia	**8**	2	1	1	3	1
Congenital haemophilia	**73**	9	44	2	6	12
Total	**169**	**30**	**79**	**12**	**18**	**30**

an arteriovenous fistula (AVF) in a 53-year-old inhibitor patient who administered rFVIIa and tranexamic acid through the AVF to treat a bleed in the palm of his hand. The patient, who was withdrawn from the trial as a result of the AVF thrombosis, had several comorbidities [18].

3.2.2. Immunogenicity

3.2.2.1. Neutralising antibodies

No confirmed cases of neutralising antibodies have been reported to date in rFVIIa-treated patients with congenital haemophilia.

3.2.2.2. Clinically non-significant binding antibodies

Low-titre, binding, non-neutralising antibodies towards rFVIIa have been detected in clinical trials involving administration of rFVIIa. In these trials, extensive antibody assessments were undertaken, with multiple assessments per patient. Five patients with haemophilia A or B tested positive for transient binding antibodies towards rFVIIa in two clinical trials involving treatment with rFVIIa; for three of the patients, the binding antibodies were already present at screening/baseline [18,29]. In addition, one case of binding, non-neutralising antibody formation towards trial product/rFVIIa was reported in a patient with haemophilia involved in a clinical trial with glycoPEGylated rFVIIa (N7-GP) [30]. A comprehensive survey of immunogenicity of rFVIIa in 267 patients over 9 years reported that non-specific, but rFVIIa-binding, non-neutralising antibodies were found in approximately 5% of patients with haemophilia A, prior to exposure to rFVIIa [31]. The binding, non-neutralising antibody results have all been of very low titre (i.e., close to the cut-off value for the assay), and there has been no effect of the low-titre antibodies on the clinical outcome, treatment efficacy or pharmacokinetics. In the cases in which there were multiple exposures to rFVIIa, the antibodies did not increase in titre with rFVIIa use.

3.3. Acquired haemophilia

3.3.1. Thrombotic events

Summaries of TEs in patients with acquired haemophilia from post-marketing data sources are detailed in Tables 2 and 3. Thirteen percent of the events reported in rFVIIa-treated patients with acquired haemophilia were TEs in the review period. An equal proportion of these TEs (39%) were either arterial or mixed (Table 2); a fatal outcome occurred in 38% of patients with one or more TEs, while 28% of patients were recovering, or had already recovered, at the time of reporting (Table 3).

Up to December 2006, TEs associated with rFVIIa in acquired haemophilia were reported in the clinical trials or pre-licensure compassionate use studies [7,8]. No clinical trials have been conducted in acquired haemophilia patients since 2006.

3.3.2. Immunogenicity

No cases of binding or neutralising antibodies against rFVIIa in acquired haemophilia patients have been reported in the clinical trials, post-marketing data sources or compassionate use programme [32,33].

3.4. Glanzmann's thrombasthenia

3.4.1. Thrombotic events

Due to the rarity of Glanzmann's thrombasthenia, no clinical trials of rFVIIa have been performed by Novo Nordisk A/S in this indication. Therefore, data on TE events are available only from post-marketing sources. Over the review period, 25% of the AEs reported in Glanzmann's thrombasthenia patients were TEs, either venous (58%) or mixed (42%) (Table 2). A fatal outcome occurred in two patients (25%) with one or more TEs; of two further patients (25%), one recovered completely and the other recovered with sequelae (Table 3).

3.4.2. Immunogenicity

No anti-rFVIIa antibodies have been reported in Glanzmann's thrombasthenia patients in post-marketing studies.

3.5. Congenital FVII deficiency

3.5.1. Thrombogenicity

Patients with congenital FVII deficiency have been reported to have a relatively high risk of developing TEs [34], especially when compared with patients suffering from other rare factor deficiencies [35,36]. In the current review, 22.5% of the AEs reported in congenital FVII deficiency patients from post-marketing sources were TEs, the majority of which (53%) were

Table 4
Thrombogenicity in congenital haemophilia with inhibitors (clinical trials): 2007–2013

	No. of patients exposed	Trial number and study design	Total no. of TEs	TE details	Reported outcomes
Morfini and Bjerre, 2011 [19]	6[a]	Phase Ib, PK and safety of original versus room temperature stable formulation of rFVIIa, 270 μg/kg	**0**	NA	NA
NN1007-1862		No bleeding episodes			
		(November 2007–June 2008)			
de Paula et al., 2012 [17]	17	Phase II, randomised, double-blind, controlled, dose-escalation study; rFVIIa used as comparator	**0**	NA	NA
NN1731-1804		19 bleeds treated			
		(June 2007–June 2010)			
		NCT00486278			
Ljung et al., 2013 [20]	23	Phase II, randomised, double-blind, dose-escalation study of N7-GP; rFVIIa was used to treat all breakthrough bleeds at the patients' normal doses	**0**	NA	NA
NN7128-1907		181+86+92 (Obs+Trt+FU) bleeds treated (=359 bleeds treated)			
		(September 2009–March 2011)			
		NCT00951405			
Lentz et al., 2014 [18]	57	Phase III, randomised, double-blind, cross-over study; rFVIIa used as a comparator	**1**	Thrombus of the arteriovenous fistula, judged by the investigator to be possibly related to rFVIIa	Fatal: 0
NN1731-3562		227 bleeds treated			Not recovered: 1
		(July 2011–August 2012)			
		NCT01392547			

NA, not available; TEs, thrombotic events; rFVIIa, recombinant activated factor VII; PK, pharmacokinetics; N7-GP, glycoPEGylated rFVIIa; Obs, observation period; Trt, treatment period; FU, follow-up period.
[a] While 24 patients with haemophilia were included in this trial, only six were congenital haemophilia patients with inhibitors.

venous (Table 2). None of the reported TEs were fatal, and more than half of the affected patients (53%) had recovered, or were recovering, at the time of data capture (Table 3).

No TE complications were recorded in the compassionate use studies that included patients with congenital FVII deficiency [37–39]. No clinical trials have been conducted on rFVIIa use in this rare bleeding disorder.

3.5.2. Immunogenicity

From post-marketing sources, 13 cases of inhibitor development were reported in 12 patients with congenital FVII deficiency (one patient had two events reported in the database). In most of these cases, the inhibitor had no clinical consequences, and treatment with rFVIIa continued to be beneficial, although higher doses were required in some cases.

In the compassionate use studies, two patients with FVII deficiency developed antibodies. The first patient was a 7-month-old girl who was given an rFVIIa dose of 800 μg/kg by mistake on the first day of a treatment episode. This patient did not suffer any TE complications, and further rFVIIa treatment was administered at the recommended dose [37]. The second patient was a 4-year-old boy who was found to have transient, low-titre alloantibodies against FVII when assayed 3 months after a single rFVIIa treatment episode. Clinical response to rFVIIa was reported to be excellent, and the antibody was most likely not inhibitory [37,39]. Both FVII-deficient patients had received plasma-derived FVII prior to rFVIIa – it is possible that antibody development may have been induced by one or both of these agents [39].

4. Discussion

This updated safety review covers data accrued on rFVIIa from its first post-licensure use, up to December 2013. Data from the compassionate use programme, which ran between 1988 and 1999 in Europe and North America [40] were also included.

A substantial body of safety data for rFVIIa has now been accumulated from clinical trials and post-marketing data, highlighting a good safety record with no unexpected safety concerns in approved indications. As expected when administering a recombinant version of the native protein, in patients without a deficiency in that protein, there have been no confirmed cases of neutralising antibodies against rFVIIa in congenital haemophilia, acquired haemophilia or Glanzmann's thrombasthenia. The data review did reveal several cases of inhibitor development in congenital FVII-deficient patients treated with rFVIIa, but this is as expected: rFVIIa is used as replacement therapy in FVII deficiency [41–44], and one of the most relevant side-effects of such replacement therapy is the development of inhibitors against FVII, regardless of the treatment used [41]. Antibody formation against FVII might therefore be reasonably anticipated [44] and indeed, a recent publication has reported the presence of inhibitors in 2.6% of FVII-deficient patients [45]. There is currently very limited information available in the literature about inhibitor formation in FVII-deficient patients, although isolated reports of FVII inhibitors associated with rFVIIa use have been published [43,44,46].

Inhibitor testing has been routinely performed for FVII-deficient patients exposed to rFVIIa as part of Novo Nordisk's post-marketing commitment. The Seven Treatment Evaluation Registry (STER) was a multicentre, prospective, observational, web-based registry established to collect data on treatment modalities and outcomes in congenital FVII deficiency [41,42]. The primary objectives of the registry were to: (i) describe treatment modalities for bleeds in a well-defined, carefully characterised, international cohort of FVII-deficient patients; (ii) study the occurrence of inhibitors/antibodies to FVII, with inhibitor testing carried out in a centralised fashion; (iii) evaluate thrombotic complications; and (iv) describe, and evaluate the efficacy of, available treatments in real-life clinical settings (including surgery) [41,42]. The STER provided the core of the pharmacovigilance surveillance programme for rFVIIa in patients with congenital FVII deficiency.

It has generally been assumed that bleeding disorders protect against the development of thrombosis and related mortality [47–51]. However, more recent data suggest that the presence of a coagulation disorder may not be protective after all: cardiovascular diseases (CVDs) are becoming more common in haemophilia patients, and the prevalence of cardiovascular risk factors is at least similar to that in the general population and, in some cases, may even be higher [52,53]. Well-established risk factors for arterial thrombosis and CVD include smoking, hypertension, obesity, high cholesterol, diabetes and a family history of CVD [21–23,47,54], and the presence of these comorbid conditions may also predispose patients with coagulation disorders to thrombosis. Furthermore, there is evidence to suggest that traditional cardiovascular risk factors may also play a role in venous thrombosis [23], and that arterial disease may directly promote venous thrombosis in certain circumstances (e.g., following stroke or myocardial infarction) [22]. As these risk factors tend to increase over time, their effects worsen with age.

These findings may explain the occurrence of TEs in patients with (often severe) coagulation disorders. While patients may be inherently anti-coagulated due to clotting factor deficiency, this protection will be reduced over time as patients age and develop risk factors, comorbid conditions and the use of central venous access devices [7] that predispose them to thrombosis. Additionally, all protective effects will be removed upon replacement of the clotting factor or restoration of normal (or near-normal) haemostasis. In this current review, only one new TE was reported in clinical trials of rFVIIa in haemophilia patients with inhibitors since 2006 (Table 4) and 84 TEs (mainly venous/mixed and non-fatal) occurred in this population across all post-marketing data sources (Table 2). In acquired haemophilia patients, 54 TEs were reported from post-marketing sources (Table 2). This is perhaps unsurprising, given that the acquired haemophilia population is typically older, with multiple underlying risk factors for thrombosis. Various combinations of age, comorbid conditions and concomitant treatment with factor concentrates or plasma-derived activated prothrombin complex concentrate have been proposed as potential contributory factors to all cases of cerebrovascular thrombosis or DIC [7].

Recombinant FVIIa is the only recombinant product available for patients with congenital FVII deficiency, thus making it the only alternative to plasma-derived products. A relatively high frequency of (particularly venous) thrombotic phenomena has previously been observed in this patient population [36], leading to the conclusion that FVII deficiency may not protect against thrombosis [36,55–58]. In line with these findings, reported TEs constitute a higher fraction of all reported AEs (22.5%) from post-marketing sources in the current review. Current literature suggests that prothrombotic risk factors are present in the majority of FVII-deficient patients with TEs [36,55–58]. Genetic factors may also play a role [55,57,58], indicating that FVII deficiency associated with thrombosis is a complex clinical scenario [58]. However, a reporting bias in relation to the post-marketing sources should perhaps also be considered as inherent to spontaneous reporting.

Finally, more safety data on rFVIIa use in older patients are available today than in previous years, collected largely through post-marketing surveillance studies [59]. As the number of elderly patients is expected to increase over time, it will be important to continue monitoring the treatment outcomes for these patients carefully. According to current knowledge, however, the safety profile in elderly haemophilia patients appears to be similar to that in the general population; importantly, no safety signals have been observed to date specifically in the elderly [60]. Due to post-marketing commitments, which include reporting safety data on rFVIIa use [9,42,60–68], our understanding of optimal therapeutic strategies in the different approved indications has increased. Indeed, the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) has published a number of guidelines on the diagnosis and treatment of haemophilia with inhibitors and rare bleeding disorders over recent years [69–72].

5. Conclusions

This review presents the largest collection of safety data available on rFVIIa use in approved indications (congenital haemophilia with inhibitors, acquired haemophilia, Glanzmann's thrombasthenia and congenital FVII deficiency). A growing body of evidence from both clinical trials and extensive post-marketing data shows that rFVIIa has a consistently favourable safety profile, with a low overall reported number of TEs compared with the estimated number of administered doses, across all approved indications. These findings can be attributed to the recombinant nature of rFVIIa and its localised mode of action: rFVIIa activates FX directly on the surface of activated platelets [12,13], which are present only at the site of injury – meaning that systemic activation of coagulation is avoided and the risk of TEs thus reduced. Nonetheless, close monitoring for signs and symptoms of TEs is warranted in all patients treated with rFVIIa (or any pro-haemostatic agent), particularly the elderly and any other patients with concomitant conditions and/or predisposing risk factors for thrombosis. The risk of inhibitor development against rFVIIa is apparently low in congenital haemophilia with inhibitors, acquired haemophilia and Glanzmann's thrombasthenia. Taken together, the findings of this updated safety review show that despite substantial use, relatively few AEs and safety concerns have occurred when rFVIIa is used in relation to its licensed indications. Recombinant FVIIa has a favourable safety profile in approved indications and is well tolerated.

Conflict of interest statement

EJ Neufeld and C Négrier have served as consultants and as advisory board members for Novo Nordisk. P Arkhammar and A Rosholm are employees of Novo Nordisk A/S, Denmark. S Benchikh el Fegoun is an employee of Novo Nordisk Health Care AG, Switzerland. S Seremetis is an employee of Novo Nordisk Inc., USA.

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References

[1] NovoSeven® Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000074/WC500030873.pdf. [Accessed March 3, 2015].
[2] NiaStase RT® Product Monograph. http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng. [Accessed April 8, 2015].
[3] NovoSeven® RT Highlights of Prescribing Information. http://www.fda.gov/downloads/.../ucm056954.pdf. [Accessed April 8, 2015].
[4] Nedergaard H, Vestergaard S, Jensen PT, Kristiansen MW, Jensen MB, Østergaard PB, et al. In vitro stability of lyophilized and reconstituted recombinant activated factor VII formulated for storage at room temperature. Clin Ther 2008;30:1309-15.

[5] Bysted BV, Scharling B, Møller T, Hansen BL. A randomized, double-blind trial demonstrating bioequivalence of the current recombinant activated factor VII formulation and a new robust 25 degrees C stable formulation. Haemophilia 2007;13:527-32.
[6] Shapiro AD, Hedner U. Advances in bypassing agent therapy for hemophilia patients with inhibitors to close care gaps and improve outcomes. Ther Adv Drug Saf 2011;2:213-25.
[7] Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. J Thromb Haemost 2004;2:899-909.
[8] Abshire T, Kenet G. Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors. Haemophilia 2008;14:898-902.
[9] Shapiro AD, Neufeld EJ, Blanchette V, Salaj P, Gut RZ, Cooper DL. Safety of recombinant activated factor VII (rFVIIa) in patients with congenital haemophilia with inhibitors: overall rFVIIa exposure and intervals following high (>240 μg kg^{-1}) rFVIIa doses across clinical trials and registries. Haemophilia 2014;20:e23-31.
[10] Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. Thromb Haemost 2001;85:958-65.
[11] Jurlander B, Thim L, Klausen NK, Persson E, Kjalke M, Rexen P, et al. Recombinant activated factor VII (rFVIIa): characterization, manufacturing, and clinical development. Semin Thromb Hemost 2001;27:373-84.
[12] Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. Br J Haematol 1997;99:542-7.
[13] Monroe DM, Hoffman M, Oliver JA, Roberts HR. A possible mechanism of action of activated factor VII independent of tissue factor. Blood Coagul Fibrinolysis 1998;9 Suppl 1:S15-20.
[14] Monroe DM, Hoffman M. What does it take to make the perfect clot? Arterioscler Thromb Vasc Biol 2006;26:41-8.
[15] Diness V, Bregengaard C, Erhardtsen E, Hedner U. Recombinant human factor VIIa (rFVIIa) in a rabbit stasis model. Thromb Res 1992;67:233-41.
[16] Gallistl S, Cvirn G, Muntean W. Recombinant factor VIIa does not induce hypercoagulability in vitro. Thromb Haemost 1999;81:245-9.
[17] de Paula EV, Kavakli K, Mahlangu J, Ayob Y, Lentz SR, Morfini M, et al. Recombinant factor VIIa analog (vatreptacog alfa [activated]) for treatment of joint bleeds in hemophilia patients with inhibitors: a randomized controlled trial. J Thromb Haemost 2012;10:81-9.
[18] Lentz SR, Ehrenforth S, Karim FA, Matsushita T, Weldingh KN, Windyga J, et al. Recombinant factor VIIa analog in the management of hemophilia with inhibitors: results from a multicenter, randomized, controlled trial of vatreptacog alfa. J Thromb Haemost 2014;12:1244-53.
[19] Morfini M, Bjerre J. Pharmacokinetics and safety of a 270 mcg kg-1 dose of room temperature stable recombinant activated factor VII in patients with haemophilia. Haemophilia 2011;17:860-6.
[20] Ljung R, Karim FA, Saxena K, Suzuki T, Arkhammar P, Rosholm A, et al. 40K glycoPEGylated, recombinant FVIIa: 3-month, double-blind, randomized trial of safety, pharmacokinetics and preliminary efficacy in hemophilia patients with inhibitors. J Thromb Haemost 2013;11:1260-8.
[21] Lijfering WM, Flinterman LE, Vandenbroucke JP, Rosendaal FR, Cannegieter SC. Relationship between venous and arterial thrombosis: a review of the literature from a causal perspective. Semin Thromb Hemost 2011;37:885-96.
[22] Lowe GD. Common risk factors for both arterial and venous thrombosis. Br J Haematol 2008;140:488-95.
[23] Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. Blood Transfus 2011;9:120-38.
[24] Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med 2014;276:618-32.
[25] Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852-66.
[26] Nowak-Göttl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, et al. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood 2001;97:858-62.
[27] Paschôa AF, Guillaumon AT. Impact of screening on thrombophilia for patients with venous thrombosis. Int Angiol 2006;25:52-9.
[28] Goldhaber SZ, Morrison RB. Cardiology patient pages. Pulmonary embolism and deep vein thrombosis. Circulation 2002;106:1436-8.
[29] Tiede A, Friedrich U, Stenmo C, Allen G, Giangrande P, Goudemand J, et al. Safety and pharmacokinetics of subcutaneously administered recombinant activated factor VII (rFVIIa). J Thromb Haemost 2011;9:1191-9.
[30] Trial ID: NN7128-380 Clinical Trial Report: Synopsis. http://novonordisk-trials.com/Website/pdf/registry/bin_20130206-034941-231.pdf. [Accessed March 25, 2015].
[31] Nicolaisen EM. Antigenicity of activated recombinant factor VII followed through nine years of clinical experience. Blood Coagul Fibrinolysis 1998;9 Suppl 1:S119-23.
[32] Arkin S, Blei F, Fetten J, Foulke R, Gilchrist GS, Heisel MA, et al. Human coagulation factor FVIIa (recombinant) in the management of limb-threatening bleeds unresponsive to alternative therapies: results from the NovoSeven emergency-use programme in patients with severe haemophilia or with acquired inhibitors. Blood Coagul Fibrinolysis 2000;11:255-9.
[33] Hay CR, Négrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. Thromb Haemost 1997;78:1463-7.
[34] Mariani G, Herrmann FH, Schulman S, Batorova A, Wulff K, Etro D, et al. Thrombosis in inherited factor VII deficiency. J Thromb Haemost 2003;1:2153-8.
[35] Girolami A, Ruzzon E, Tezza F, Scandellari R, Vettore S, Girolami B. Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review. Haemophilia 2006;12:345-51.
[36] Girolami A, Tezza F, Scandellari R, Vettore S, Girolami B. Associated prothrombotic conditions are probably responsible for the occurrence of thrombosis in almost all patients with congenital FVII deficiency. Critical review of the literature. J Thromb Thrombolysis 2010;30:172-8.
[37] Mariani G, Konkle BA, Ingerslev J. Congenital factor VII deficiency: therapy with recombinant activated factor VII – a critical appraisal. Haemophilia 2006;12:19-27.
[38] Rice KM, Savidge GF. NovoSeven (recombinant factor VIIa) in central nervous systems bleeds. Haemostasis 1996;26(Suppl. 1):131-4.
[39] Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. Haemophilia 1999;5:253-9.
[40] Sumner MJ, Geldziler BD, Pedersen M, Seremetis S. Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. Haemophilia 2007;13:451-61.
[41] Mariani G, Lapecorella M, Dolce A. Steps towards an effective treatment strategy in congenital factor VII deficiency. Semin Hematol 2006;43:S42-7.
[42] Mariani G, Dolce A, Batorova A, Auerswald G, Schved JF, Siragusa S, et al. Recombinant, activated factor VII for surgery in factor VII deficiency: a prospective evaluation – the surgical STER. Br J Haematol 2011;152:340-6.
[43] Tokgoz H, Caliskan U, Lavigne-Lissalde G, Giansily-Blaizot M. Successful prophylactic use of recombinant activated factor VII (rFVIIa) in a patient with congenital FVII deficiency and inhibitors to FVII. Haemophilia 2012;18:e25-7.
[44] Nicolaisen EM. Long-term follow-up with regard to potential immunogenicity: clinical experience with NovoSeven (recombinant factor VIIa). Haemostasis 1996;26(Suppl. 1):98-101.
[45] Batorova A, Mariani G, Kavakli K, De Saez AR, Caliskan U, Karimi M, et al. Inhibitors to factor VII in congenital factor VII deficiency. Haemophilia 2014;20:e188-91.
[46] Pruthi RK, Rodriguez V, Allen C, Slaby JA, Schmidt KA, Plumhoff EA. Molecular analysis in a patient with severe factor VII deficiency and an inhibitor: report of a novel mutation (S103G). Eur J Haematol 2007;79:354-9.
[47] Biere-Rafi S, Zwiers M, Peters M, van der Meer J, Rosendaal FR, Buller HR, et al. The effect of haemophilia and von Willebrand disease on arterial thrombosis: a systematic review. Neth J Med 2010;68:207-14.
[48] Bilora F, Zanon E, Petrobelli F, Cavraro M, Prandoni P, Pagnan A, et al. Does hemophilia protect against atherosclerosis? A case-control study. Clin Appl Thromb Hemost 2006;12:193-8.
[49] Gailani D, Renné T. Intrinsic pathway of coagulation and arterial thrombosis. Arterioscler Thromb Vasc Biol 2007;27:2507-13.
[50] Rosendaal FR, Briet E, Stibbe J, van Herpen G, Leuven JA, Hofman A, et al. Haemophilia protects against ischaemic heart disease: a study of risk factors. Br J Haematol 1990;75:525-30.
[51] Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19:e1-47.
[52] de Raucourt E, Roussel-Robert V, Zetterberg E. Prevention and treatment of atherosclerosis in haemophilia – how to balance risk of bleeding with risk of ischaemic events. Eur J Haematol 2015;94 Suppl. 77:23-9.
[53] Staritz P, de Moerloose P., Schutgens R, Dolan G, ADVANCE Working Group. Applicability of the European Society of Cardiology guidelines on management of acute coronary syndromes to people with haemophilia – an assessment by the ADVANCE Working Group. Haemophilia 2013;19:833-40.
[54] Schutgens RE, Tuinenburg A, Fischer K, Mauser-Bunschoten EP. Anti-coagulation therapy in haemophilia. Managing the unknown. Hamostaseologie 2013;33:299-304.
[55] Giansily-Blaizot M, Marty S, Chen SW, Pellequer JL, Schved JF. Is the coexistence of thromboembolic events and Factor VII deficiency fortuitous? Thromb Res 2012;130(Suppl. 1):S47-9.
[56] Girolami A, Bertozzi I, Rigoni I, Muzzolon R, Vettore S. Congenital FVII deficiency and thrombotic events after replacement therapy. J Thromb Thrombolysis 2011;32:362-7.
[57] Girolami A, Berti de Marinis G, Vettore S, Girolami B. Congenital FVII deficiency and pulmonary embolism: a critical appraisal of all reported cases. Clin Appl Thromb Hemost 2013;19:55-9.
[58] Marty S, Barro C, Chatelain B, Fimbel B, Tribout B, Reynaud J, et al. The paradoxical association between inherited factor VII deficiency and venous thrombosis. Haemophilia 2008;14:564-70.
[59] Bleeding disorder statistics for April 2013 to March 2014. A report from the National Haemophilia Database. http://www.ukhcdo.org/docs/AnnualReports/2014/Bleeding_Disorder_Statistics_For_Website_2013-2014.pdf. [Accessed March 25, 2015].
[60] Dolan G, Bjerre J, Hay CRM. Real-life use of activated recombinant FVII (rFVIIa)

in elderly patients with haemophilia with inhibitors – data from the UK National Haemophilia Database. J Thromb Haemost 2013;11(Suppl. 2):980.
[61] Birschmann I, Klamroth R, Eichler H, Schenk J, Kirchmaier CM, Halimeh S. Results of the WIRK prospective, non-interventional observational study of recombinant activated factor VII (rFVIIa) in patients with congenital haemophilia with inhibitors and other bleeding disorders. Haemophilia 2013;19:679-85.
[62] Chambost H, Santagostino E, Laffan M, Kavakli K, ONE Registry Steering Committee on behalf of the investigators. Real-world outcomes with recombinant factor VIIa treatment of acute bleeds in haemophilia patients with inhibitors: results from the international ONE registry. Haemophilia 2013;19:571-7.
[63] Di Minno G, d'Oiron R, Zotz R, Poon M-C. Treatment modalities and outcomes in 870 non-surgical bleeds in 184 Glanzmann's thrombasthenia patients: the International Prospective Glanzmann's Thrombasthenia Registry. Haematologica 2015;May 22. pii:haematol.2014.121475.
[64] Hay CRM, Bjerre J, Dolan G. Real-life use of high and standard initial doses of activated recombinant factor VII (rFVIIa) in patients with haemophilia A and B with inhibitors – data from the UKHCDO/NHD registry. J Thromb Haemost 2013;11(Suppl. 2):718.
[65] Kavakli K, Arkhammar P, Benson G, Chambost H, De Martis F, Rosholm A. Interim results from the prospective observational study on NovoSeven® room temperature stable (VII25) in patients with hemophilia A or B. J Thromb Haemost 2014;12(Suppl. 1):63-4.
[66] Mariani G, Dolce A, Napolitano M, Ingerslev J, Giansily-Blaizot M, Di Minno MD, et al. Invasive procedures and minor surgery in factor VII deficiency. Haemophilia 2012;18:e63-5.
[67] Napolitano M, Giansily-Blaizot M, Dolce A, Schved JF, Auerswald G, Ingerslev J, et al. Prophylaxis in congenital factor VII deficiency: indications, efficacy and safety. Results from the Seven Treatment Evaluation Registry (STER). Haematologica 2013;98:538-44.
[68] Poon M-C, d'Oiron R, Zotz R, Di Minno G. Treatment modalities and outcomes in 204 surgical procedures in 96 Glanzmann's thrombasthenia (GT) patients: the International Prospective Glanzmann's Thrombasthenia Registry (GTR). Haematologica 2015;May 22. pii:haematol.2014.121384.
[69] Bolton-Maggs PH, Chalmers EA, Collins PW, Harrison P, Kitchen S, Liesner RJ, et al. A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Br J Haematol 2006;135:603-33.
[70] Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. Br J Haematol 2013;160:153-70.
[71] Collins W, Chalmers E, Hart D, Jennings I, Liesner R, Rangarajan S, et al. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. Br J Haematol 2013;162:758-73.
[72] Mumford AD, Ackroyd S, Alikhan R, Bowles L, Chowdary P, Grainger J, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol 2014;167:304-26.
[73] Al-Mondhiry HAB, Ma A, Kessler CM, Fisher M, Gut RZ, Cooper DL. US experience with recombinant factor VIIa (rFVIIa) for surgery in acquired hemophilia (AH): analysis from the Hemostasis and Thrombosis Research Society (HTRS) registry. Blood 2012;120:3372.
[74] Ma A, Kessler CM, Gut RZ, Cooper DL. Recombinant factor VIIa (rFVIIa) is safe and effective when used to treat acute bleeding episodes and to prevent bleeding during surgery in patients with acquired hemophilia: updated assessment from the Hemostasis and Thrombosis Research Society (HTRS) registry AH database. Blood 2011;118:3374.
[75] Ma AD, Kessler C, Al-Mondhiry HAB, Fisher M, Gut RZ, Cooper DL. Use of recombinant factor VIIa (rFVIIa) for acute bleeding episodes in acquired haemophilia: final analysis from the Hemostasis and Thrombosis Research Society (HTRS) registry AH study. Blood 2012;120:4264.
[76] Parameswaran R, Shapiro AD, Gill JC, Kessler CM, HTRS Registry Investigators. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. Haemophilia 2005;11:100-6.
[77] Takedani H, Shima M, Horikoshi Y, Koyama T, Fukutake K, Kuwahara M, et al. Ten-year experience of recombinant activated factor VII use in surgical patients with congenital haemophilia with inhibitors or acquired haemophilia in Japan. Haemophilia 2014 Dec 18 [Epub ahead of print].
[78] Young G, Shapiro AD, Walsh CE, Gruppo RA, Gut RZ, Cooper DL. Patient/caregiver-reported recombinant factor VIIa (rFVIIa) dosing: home treatment of acute bleeds in the Dosing Observational Study in Hemophilia (DOSE). Haemophilia 2012;18:392-9.
[79] Young G, Auerswald G, Jimenez-Yuste V, Lambert T, Morfini M, Santagostino E, et al. PRO-PACT: retrospective observational study on the prophylactic use of recombinant factor VIIa in hemophilia patients with inhibitors. Thromb Res 2012;130:864-70.
[80] Belhani MF, Hadj Khalifa H, Wali YAS, Alzoebie A, Saad HA, Benchikh el Fegoun S. Home treatment of haemarthrosis with activated recombinant factor VII (rFVIIa) in haemophilia A and B patients with inhibitors: a prospective observational study. Haemophilia 2013;19(Suppl. 2):43.
[81] Shapiro AD, Akins S, Cooper DL. Long-term outcomes from orthopaedic surgery in haemophilia: are we measuring success and documenting and assessing complications? Haemophilia 2014;20:e367-71.