

IQWiG Reports – Commission No. A15-54

**Efmoroctocog alfa –  
Benefit assessment according to  
§35a Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of Sections 2.1 to 2.6 of the dossier assessment *Efmoroctocog alfa – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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<sup>3</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

## **2 Benefit assessment**

### **2.1 Executive summary of the benefit assessment**

#### **Background**

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug efmoroctocog alfa. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 18 December 2015.

#### **Research question**

The aim of the present report was to assess the added benefit of efmoroctocog alfa compared with the appropriate comparator therapy (ACT) in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The G-BA specified the ACT for the therapeutic indication as follows:

- recombinant or human plasma-derived coagulation factor VIII products

In its choice of the ACT, the company followed the G-BA’s specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. The minimum study duration for prophylactic treatment is 6 months. A study duration of at least 50 exposure days has to be guaranteed for an assessment of on-demand treatment.

#### **Results**

The company presented no relevant data for the assessment of the added benefit of efmoroctocog alfa versus the ACT.

#### ***Direct comparison***

From its information retrieval, the company identified no randomized or non-randomized study of direct comparison on the comparison of efmoroctocog alfa with the ACT, neither for prophylaxis nor for on-demand treatment.

#### ***Further investigations***

Since comparative studies were lacking, the company conducted an unadjusted historical comparison for the derivation of the added benefit of efmoroctocog alfa in comparison with the ACT, which only referred to prophylactic treatment, however. The study pool of the company to prove the added benefit of efmoroctocog alfa comprised a total of 8 studies, one study on efmoroctocog alfa and 7 studies on the comparator therapy. The unadjusted historical comparison presented was unsuitable for the assessment of the added benefit of

efmoroctocog alfa because it was based on an incomplete study pool and was inadequate with regard to content.

On the one hand, the company did not implement its own research question for the ACT because it limited the inclusion criteria regarding the population (only patients aged 12 years and older with moderate to severe haemophilia) and the comparator therapy (only recombinant factor VIII products). Furthermore, the company limited its analyses to the 2 outcomes “annualized bleeding episodes” and “consumption of factor VIII products”. However, all available results from the outcome categories “mortality”, “morbidity”, “health-related quality of life” and “adverse events” have to be principally used for the benefit assessment.

On the other hand, the information retrieval for the ACT was incorrect and therefore incomplete: The bibliographical literature search and the selection were unsuitable; the search in trial registries was lacking completely. A simplified search already identified several studies that are potentially relevant for the company’s research question.

### ***Summary***

Overall, the company presented no relevant data for the assessment of the added benefit of efmoroctocog alfa. Hence there was no hint of an added benefit of efmoroctocog alfa in comparison with the ACT; the added benefit of efmoroctocog alfa is not proven.

### **Extent and probability of added benefit, patient groups with therapeutically important added benefit<sup>4</sup>**

On the basis of the results presented, the extent and probability of the added benefit of the drug efmoroctocog alfa compared with the ACT is assessed as follows:

Table 2 presents a summary of the extent and probability of the added benefit of efmoroctocog alfa.

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<sup>4</sup> On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].



Table 2: Efmoroctocog alfa – extent and probability of added benefit

Therapeutic indication	ACT <sup>a</sup>	Extent and probability of added benefit
Treatment and prophylaxis of bleeding in children and adults with haemophilia A (congenital factor VIII deficiency)	<b>Recombinant or human plasma-derived coagulation factor VIII products</b>	Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.</p> <p>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

The G-BA decides on the added benefit.

## 2.2 Research question

The aim of the present report was to assess the added benefit of efmoroctocog alfa compared with the ACT in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The G-BA specified the ACT for the therapeutic indication as follows:

- recombinant or human plasma-derived coagulation factor VIII products

In its choice of the ACT, the company followed the G-BA's specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. The minimum study duration for prophylactic treatment is 6 months. A study duration of at least 50 exposure days has to be guaranteed for an assessment of on-demand treatment.

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on efmoroctocog alfa (status: 1 October 2015)
- bibliographical literature search on efmoroctocog alfa (last search on 12 October 2015)
- search in trial registries for studies on efmoroctocog alfa (last search on 1 October 2015)
- bibliographical literature search on the ACT (last search on 12 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on efmoroctocog alfa (last search on 18 January 2016)
- simplified search for studies on the ACT for the unadjusted historical comparison (last search on 3 February 2016)

### Direct comparison

From its information retrieval, the company identified no randomized or non-randomized study of direct comparison on the comparison of efmoroctocog alfa with the ACT, neither for prophylaxis nor for on-demand treatment. The check of completeness also produced no study of direct comparison.

### Further investigations

Since comparative studies were lacking, the company conducted an unadjusted historical comparison for the derivation of the added benefit of efmoroctocog alfa in comparison with the ACT, which only referred to prophylactic treatment, however. The study pool of the

company comprised a total of 8 studies, one study on efmoroctocog alfa (study 997HA301 [3]) and 7 studies on the comparator therapy (Tarantino 2004 [4], Shapiro 2007 [5], Valentino 2012 [6], Recht 2009 [7], Lentz 2013 [8], Tiede 2013 [9] and Pollmann 2007 [10]).

The unadjusted historical comparison presented was unsuitable for the assessment of the added benefit of efmoroctocog alfa because it was based on an incomplete study pool and was inadequate with regard to content. The reasons for this are as follows:

- The investigation of the research question was incomplete with regard to content: The company limited the inclusion criteria for the search of studies on the ACT regarding the population (only patients aged 12 years and older with moderate to severe haemophilia) and the comparator therapy (only recombinant factor VIII products). The company's implementation of its own research question on the side of the comparator therapy was therefore incomplete with regard to content; and the criteria were unsuitable to identify a study pool complete for the research question (see Section 2.7.2.1 of the full dossier assessment). Furthermore, the company limited its analyses to the 2 outcomes "annualized bleeding episodes" and "consumption of factor VIII products". However, all available results from the outcome categories "mortality", "morbidity", "health-related quality of life" and "adverse events" have to be principally used for the benefit assessment.
- The search for studies with the comparator therapy was incomplete and incorrect: On the one hand, the company did not conduct the search in trial registries for studies with the ACT required by the dossier templates. On the other, the bibliographical literature search on studies with the ACT conducted by the company had numerous deficiencies, making it unsuitable to guarantee a complete study pool (see Section 2.7.2.3.1 of the full dossier assessment). For example, one of the publications (Shapiro 2007 [5]) cited as relevant by the company cannot be identified with the search strategy documented by the company. A simplified search identified additional potentially relevant studies on recombinant factor VIII products (Collins 2010 [11] and Powell 2012 [12]), which the company did not consider in its analysis.
- The study selection was inadequate: In the framework of its study selection, the company excluded several references of potentially relevant studies both on efmoroctocog alfa and on recombinant factor VIII products from its study pool, which met all of the company's inclusion criteria, however. For efmoroctocog alfa, the company included its approval study 997HA301 [3], but not its extension study 8HA01EXT [13]. For recombinant factor VIII products, the company excluded the SPINART study [14], the POTTER study [15] and Parra Lopez 2015 [16], for example.

### ***Inconsistent information in the dossier***

It should also be noted that large parts of the dossier submitted by the company were inconsistent. This particularly concerned the formulation of inclusion and exclusion criteria for the identification of studies on the comparator therapy deviating from the research question (see Section 2.7.2.1 of the full dossier assessment) and information on the selection criteria used.

This was possibly caused by the fact that the company ultimately based the derivation of the added benefit of efmoroctocog alfa in Module 4 A on analyses from a manuscript, which has not been published yet (Iorio [17]). The analysis contained in this manuscript does not meet the content requirements of the early benefit assessment, however. The research question investigated by the company in its further investigations, the scope of the study pool resulting from the information retrieval, and the results on only 2 benefit outcomes considered patient-relevant by the company that were used for the derivation of the added benefit of efmoroctocog alfa were identical to the presentations in Iorio; analyses on adverse events, for example, were lacking both in the manuscript and in the dossier. The corresponding data would have been available to the company from the identified primary publications on studies on the ACT or from the clinical study reports on efmoroctocog alfa, however.

## 2.4 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of efmoroctocog alfa in its dossier. Hence the added benefit of efmoroctocog alfa versus the ACT is not proven.

This result deviates from the assessment of the company, which derived an added benefit from the studies it included.

## 2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of efmoroctocog alfa in comparison with the ACT is shown in Table 3.

Table 3: Efmoroctocog alfa – extent and probability of added benefit

Therapeutic indication	ACT <sup>a</sup>	Extent and probability of added benefit
Treatment and prophylaxis of bleeding in children and adults with haemophilia A (congenital factor VIII deficiency)	<b>Recombinant or human plasma-derived coagulation factor VIII products</b>	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This deviates from that of the company's approach, which derived a hint of a non-quantifiable added benefit of efmoroctocog alfa.

The G-BA decides on the added benefit.

## 2.6 List of included studies

Not applicable because the company presented no relevant data for the assessment of the added benefit of efmoroctocog alfa.

## References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22 April 2015 [accessed: 20 October 2015]. URL: [https://www.iqwig.de/download/IQWiG\\_General\\_Methods\\_Version\\_%204-2.pdf](https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf).
2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58
3. Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014; 123(3): 317-325.
4. Tarantino MD, Collins PW, Hay CR, Shapiro AD, Gruppo RA, Berntorp E et al. Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia* 2004; 10(5): 428-437.
5. Shapiro AD. Anti-hemophilic factor (recombinant), plasma/albumin-free method (octocog-alpha; ADVATE) in the management of hemophilia A. *Vasc Health Risk Manag* 2007; 3(5): 555-565.
6. Valentino LA, Mamonov V, Hellmann A, Quon DV, Chybicka A, Schroth P et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost* 2012; 10(3): 359-367.
7. Recht M, Nemes L, Matysiak M, Manco-Johnson M, Lusher J, Smith M et al. Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII. *Haemophilia* 2009; 15(4): 869-880.
8. Lentz SR, Misgav M, Ozelo M, Salek SZ, Veljkovic D, Recht M et al. Results from a large multinational clinical trial (guardian1) using prophylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia A: safety and efficacy. *Haemophilia* 2013; 19(5): 691-697.
9. Tiede A, Knaub S, Oldenburg J, Bichler J. Consumption of FVIII concentrate during on-demand and prophylactic treatment with human-cl rhFVIII In prospective clinical studies in adult patients with severe hemophilia A [online]. In: 55th ASH Annual Meeting and Exposition; 7 – 10 December 2013; New Orleans, USA. URL: <https://ash.confex.com/ash/2013/webprogram/Paper61138.html>.

10. Pollmann H, Externest D, Ganser A, Eifrig B, Kreuz W, Lenk H et al. Efficacy, safety and tolerability of recombinant factor VIII (REFACTO) in patients with haemophilia A: interim data from a postmarketing surveillance study in Germany and Austria. *Haemophilia* 2007; 13(2): 131-143.
11. Collins P, Faradji A, Morfini M, Enriquez MM, Schwartz L. Efficacy and safety of secondary prophylactic vs. on-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia A: results from a 13-month crossover study. *J Thromb Haemost* 2010; 8(1): 83-89.
12. Powell J, Martinowitz U, Windyga J, Di Minno G, Hellmann A, Pabinger I et al. Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients: a randomised, active-controlled, double-blind study. *Thromb Haemost* 2012; 108(5): 913-922.
13. Biogen. Long-term safety and efficacy of rFVIII-Fc in the prevention and treatment of bleeding episodes in previously treated participants with hemophilia A (ASPIRE): full text view [online]. In: *ClinicalTrials.gov*. 14 January 2016 [accessed: 17 February 2016]. URL: <https://clinicaltrials.gov/ct2/show/study/NCT01454739>.
14. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L et al. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *J Thromb Haemost* 2013; 11(6): 1119-1127.
15. Tagliaferri A, Feola G, Molinari AC, Santoro C, Rivolta GF, Cultrera DB et al. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost* 2015; 114(1): 35-45.
16. Parra Lopez R, Nemes L, Jimenez-Yuste V, Rusen L, Cid AR, Charnigo RJ et al. Prospective surveillance study of haemophilia A patients switching from moroctocog alfa or other factor VIII products to moroctocog alfa albumin-free cell culture (AF-CC) in usual care settings. *Thromb Haemost* 2015; 114(4): 676-684.
17. Iorio A, Krishnan S, Myrén KJ, Lethagen S, McCormick N, Yermakov S et al. Indirect comparisons of efficacy and factor consumption during routine prophylaxis with recombinant factor VIII Fc fusion protein and other recombinant factor VIII products [eingereichtes Manuskript]. 2015.

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