IQWiG Reports – Commission No. A19-58

Turoctocog alfa pegol (haemophilia A) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Turoctocog alfa pegol (Hämophilie A) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 October 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
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 turoctocog alfa pegol. 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 31 July 2019.

Research question

The aim of this report was to assess the added benefit of turoctocog alfa pegol in comparison with recombinant or human plasma-derived coagulation factor VIII products as appropriate comparator therapy (ACT) in patients with haemophilia A.

The research question for the benefit assessment presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of turoctocog alfa pegol

Research question	Subindication	ACT[a]
1	treatment and prophylaxis of bleeding in patients 12 years and older with haemophilia A (congenital factor VIII deficiency)	recombinant or human plasma-derived coagulation factor VIII products
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company determined both recombinant and human plasma-derived factor VIII products as ACT and thus followed the options specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of 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 the episodic treatment.

Results

Direct comparison

The company identified no randomized or non-randomized studies on the direct comparison of turoctocog alfa pegol with the ACT, neither for prophylaxis nor for episodic treatment. The check of completeness also produced no study of direct comparison.

Further investigations

The company included the non-comparative studies Pathfinder 2 and Pathfinder 3 in its study pool. It conducted no search for studies with the ACT.

The Pathfinder 2 study is an open-label, non-controlled study which included pretreated patients aged 12 years and older with severe haemophilia A. In the study, a total of 186 male patients received either prophylactic or episodic treatment with turoctocog alfa pegol, as appropriate. In its dossier, the company only considered the prophylactically treated patients.

The Pathfinder 3 study is a single-arm, non-comparative study investigating turoctocog alfa pegol in bleeding management during surgery. For this purpose, the study included 34 participants of Pathfinder 2 who had to undergo major surgery.

Both studies presented by the company were unsuitable for the derivation of an added benefit, because as non-controlled studies they enabled no comparison with the ACT. The fact that the company did not search for studies on the ACT results in an incomplete study pool in terms of content and to the fact that the research question of the present benefit assessment cannot be answered.

In its dossier, the company only provided a descriptive presentation of the data of the Pathfinder 3 study. The company did not aim to conduct a comparison with the ACT.

Based on Pathfinder 2, the company conducted a comparison of the prophylactic study treatment with turoctocog alfa pegol versus individual prophylactic treatment with other recombinant or human plasma-derived factor VIII products administered before the start of the study. This prophylaxis received before the start of the study had thus not been performed under study conditions. The fact that the company did not search for studies on the ACT cannot be remedied by a before-after comparison as with the Pathfinder 2 study. The therapy implemented under study conditions cannot be compared with prophylactic treatment outside the study situation. Nevertheless, the company performed its before-after comparisons only for benefit outcomes, but not for outcomes on side effects.

Results on added benefit

The company presented no suitable data for the assessment of the added benefit of turoctocog alfa pegol. This resulted in no hint of an added benefit of turoctocog alfa pegol in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of turoctocog alfa pegol.

Table 3: Turoctocog alfa pegol – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
treatment and prophylaxis of bleeding in patients 12 years and older with haemophilia A (congenital factor VIII deficiency)	recombinant or human plasma-derived coagulation factor VIII products	added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of turoctocog alfa pegol in comparison with recombinant or human plasma-derived coagulation factor VIII products as ACT in patients with haemophilia A.

The research question for the benefit assessment presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of turoctocog alfa pegol

Research question	Subindication	ACT[a]
1	treatment and prophylaxis of bleeding in patients 12 years and older with haemophilia A (congenital factor VIII deficiency)	recombinant or human plasma-derived coagulation factor VIII products
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

The company determined both recombinant and human plasma-derived factor VIII products as ACT and thus followed the options specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of 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 the episodic 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 turoctocog alfa pegol (status: 15 May 2019)
- bibliographical literature search on turoctocog alfa pegol (last search on 3 June 2019)
- search in trial registries for studies on turoctocog alfa pegol (last search on 4 June 2019)

To check the completeness of the study pool:

- search in trial registries for studies on turoctocog alfa pegol (last search on 15 August 2019)

No relevant study was identified from the check.

Direct comparison

The company identified no randomized or non-randomized studies on the direct comparison of turoctocog alfa pegol with the ACT, neither for prophylaxis nor for episodic treatment. The check of completeness also produced no study of direct comparison.

Further investigations

The company included the non-comparative studies Pathfinder 2 [3-6] and Pathfinder 3 in its study pool [7]. It conducted no search for studies with the ACT.

Pathfinder 2

The Pathfinder 2 study is an open-label, non-controlled study which included pretreated patients aged 12 years and older with severe haemophilia A (factor VIII activity < 1%). The study was divided into a main phase (7 to 19 months) and two extension phases (65 months in total).

In the main phase, a total of 186 male patients received either prophylactic or episodic treatment with turoctocog alfa pegol, as appropriate. Prophylaxis was implemented with 50 IU/kg, every four days or twice weekly, for a total of at least 50 exposure days in 175 patients. One patient changed the treatment regimen and was thus considered in both treatment arms.

Moreover, 12 patients received no prophylaxis, but episodic treatment for acute bleeding. The dosage was 20 to 75 IU/kg, as appropriate.

However, in module 4 A of its dossier, the company did not consider the 12 patients treated for acute bleeding, but derived the added benefit of turoctocog alfa pegol exclusively on the basis of the prophylactically treated patients.

In the first extension phase, suitable patients were randomized to one of two dosing intervals for prophylaxis. They received turoctocog alfa pegol either every four or every seven days. Dosage at 7-day intervals was 75 UE/kg. Patients who had ≥ 2 bleedings had to change back to 4-day intervals. In the second extension phase, patients undergoing prophylaxis could switch between the 4-day and the 7-day application intervals depending on the frequency of their bleeding episodes.

Pathfinder 3

Pathfinder 3 is a non-comparative study investigating turoctocog alfa pegol in bleeding management during surgery. For this purpose, the study included 34 participants of Pathfinder 2 who had to undergo major surgery. Such major surgery includes all invasive interventions in which a body cavity or fascial layer had been opened, a mesenchymal barrier had been passed, an organ had been removed or the normal anatomy had been changed. The surgeries had to require substitution with factor VIII products over several days.

The turoctocog alfa pegol dose was specified depending on the factor VIII activity level and the severity of the surgery according to the guidelines of the World Federation of Haemophilia (WFH) [8]. Treatment was performed before the intervention as well as up to 14 days after surgery.

Studies of the company were not relevant for the derivation of an added benefit

Both studies of the company are not suitable for a derivation of an added benefit, because, being non-controlled studies, they enable no comparison with the ACT. The fact that the company did not search for studies on the ACT results in an incomplete study pool and in the fact that the research question of the present benefit assessment cannot be answered (see Section 2.6.3.1 of the full benefit assessment).

Study Pathfinder 3

The company only provided a descriptive presentation of the results of Pathfinder 3. A comparison with the ACT was not performed in the study and was not otherwise aspired by the company.

Before-after comparison by the company on the basis of the Pathfinder 2 study

Based on Pathfinder 2, the company conducted a comparison of the prophylactic study treatment with turoctocog alfa pegol versus individual prophylactic treatment with other recombinant or human plasma-derived factor VIII products administered before the start of the

study. Moreover, the company presented results for a subpopulation of patients coming from OECD countries formed post hoc. In doing so, the company wanted to address the transferability to the German health care context. According to the company, the patients of this population had received approval-compliant long-term prophylaxis both during the study and in the prior therapy.

The fact that the company did not search for studies investigating the ACT cannot be remedied by a before-after comparison as performed with the Pathfinder 2 study. The therapy implemented under study conditions cannot be compared with prophylactic treatment outside the study situation. This applies irrespective of the question whether the pretreatment was performed adequately. Nevertheless, the company performed its before-after comparisons only for benefit outcomes (annualized bleeding rate (ABR), health status, health-related quality of life) but not for outcomes on side effects.

For its before-and-after comparisons, the company presented the results both for the total population of the Pathfinder 2 study and separately for adolescents and adults as well as for the OECD population formed by it. It conducted the before-after comparison under consideration of the different phases of the Pathfinder 2 study (= after data). Regardless of the lack of suitability of the before-after data, the differences presented by the company are too small to derive an effect in favour of turoctocog alfa pegol. Moreover, the results are not statistically significant or relevant for the annualized bleeding rate and other outcomes. This applies to the total population and to the subpopulation formed by the company.

Results on added benefit

The company presented no suitable data for the assessment of the added benefit of turoctocog alfa pegol. This resulted in no hint of an added benefit of turoctocog alfa pegol in comparison with the ACT; an added benefit is therefore not proven.

2.4 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of turoctocog alfa pegol in comparison with the ACT.

Table 5: Turoctocog alfa pegol – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
treatment and prophylaxis of bleeding in patients 12 years and older with haemophilia A (congenital factor VIII deficiency)	recombinant or human plasma-derived coagulation factor VIII products	added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for turoctocog alfa pegol.

The G-BA decides on the added benefit.

2.5 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2019/a19-58-turoctocog-alfa-pegol-nutzenbewertung-gemaess-35a-sgb-v.12494.html.