IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Nonacog beta pegol (haemophilia B) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nonacog beta pegol (Hämophilie B) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 January 2018). 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)
IU	international units
RCT	randomized controlled trial
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 nonacog beta 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 27 October 2017.

Research question

The aim of the present report was to assess the added benefit of nonacog beta pegol in comparison with the appropriate comparator therapy (ACT) in the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency).

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

Table 2: Research question of the benefit assessment of nonacog beta pegol

Research question	Therapeutic indication	ACT[a]
1	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency)	**Recombinant or human plasma-derived coagulation factor IX products**

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

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

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 is adequate for an assessment of on-demand treatment.

Results

The company presented no relevant data for the assessment of the added benefit of nonacog beta pegol 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 nonacog beta pegol with the ACT, neither for prophylaxis nor for on-demand treatment.

Further investigations

In its study pool, the company considered the randomized controlled trial (RCT) NN7999-3747 and the corresponding extension study NN7999-3775 for nonacog beta pegol.

In the NN7999-3747 study, pretreated patients with moderate or severe haemophilia B aged 13 to 70 years were allocated to either prophylactic or on-demand treatment with nonacog beta pegol. The decision on the allocation to the respective therapeutic strategy (prophylactic or on-demand) was taken jointly by the patient and the investigator. Patients allocated to prophylactic study treatment were randomized either to a low-dose arm or to a high-dose arm. Hence the NN7999-3747 study had a total of 3 treatment arms. After completion of the NN7999-3747 study, all patients had the possibility to switch to the NN7999-3775 extension study and continue their respective treatment with nonacog beta pegol for an additional period of at least 12 months.

Since all patients in the NN7999-3747 study were treated with nonacog beta pegol and there was no control arm for conducting an adjusted indirect comparison, the company tried to derive an added benefit from different analyses of individual arms of its studies NN7999-3747 and NN7999-3775:

- Before-after comparison: The company compared the treatment effect of a prophylactic study treatment with nonacog beta pegol versus prophylactic treatment with recombinant or human plasma-derived coagulation factor IV products received before the start of the study.
- "Improvement not yet achieved in the actual health care setting": The company described considering the "absolute extent of the effect" (of individual study arms on nonacog beta pegol) as measure for the added benefit. According to the company, this approach was particularly suitable for outcomes in which nonacog beta pegol achieved an "improvement not yet achieved in the actual health care setting" in the sense of a "dramatic" effect.

However, no added benefit of nonacog beta pegol could be derived from the analyses presented by the company because these were inadequate with regard to content and, in addition, were based on an incomplete study pool.

For its before-after comparison, the company used results on patients who had received approval-compliant long-term prevention in its studies NN7999-3747 and NN7999-3775 and who also had received prophylactic treatment in the framework of their individual care already before the start of the study. However, the treatment conducted under study conditions can obviously not be compared to prophylactic treatment outside the study situation. This is

irrespective of the question whether the pretreatment was provided adequately. Examples of studies with different coagulation factor IX products (nonacog alfa, albutrepenonacog alfa, and nonacog beta pegol) showed annual bleeding rates of similar magnitudes under study conditions. Hence not only the company's before-after comparison was not informative, but the company's approach of showing "improvements not yet achieved in the actual health care setting" for individual outcomes was also refuted.

In addition, the company conducted no information retrieval for the ACT. Hence the company's information retrieval on further investigations was incomplete with regard to content and unsuitable for a comparison between nonacog beta pegol and the comparator therapy.

Summary

Overall, the company presented no relevant data for the assessment of the added benefit of nonacog beta pegol. Hence there was no hint of an added benefit of nonacog beta 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]

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

Table 3 presents a summary of the probability and extent of the added benefit of nonacog beta pegol.

Table 3: Nonacog beta pegol – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency)	**Recombinant or human plasma-derived coagulation factor IX products**	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		

[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 G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of nonacog beta pegol in comparison with the ACT in the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency).

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

Table 4: Research question of the benefit assessment of nonacog beta pegol

Research question	Therapeutic indication	ACT[a]
1	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency)	**Recombinant or human plasma-derived coagulation factor IX products**

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

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

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 is adequate 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 lists on nonacog beta pegol (status: 6 October 2017)
- bibliographical literature search on nonacog beta pegol (last search on 24 August 2017)
- search in trial registries for studies on nonacog beta pegol (last search on 6 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on nonacog beta pegol (last search on 13 November 2017)

Direct comparison

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

Further investigations

In its study pool, the company considered the studies NN7999-3747 [3,4] and NN7999-3775 [5,6], which had no active control. In the NN7999-3747 study, pretreated patients with moderate or severe haemophilia B aged 13 to 70 years were allocated to either prophylactic or on-demand treatment with nonacog beta pegol. The decision on the allocation to the respective therapeutic strategy (prophylactic or on-demand) was taken jointly by the patient and the investigator. Patients allocated to prophylactic study treatment were randomized either to a low-dose arm (10 international units [IU] per kg body weight once weekly) or to a high-dose arm (40 IU per kg body weight once weekly). Hence the NN7999-3747 study had a total of 3 treatment arms. The treatment period with nonacog beta pegol in the NN7999-3747 study was 52 weeks for patients allocated to prophylactic treatment. For patients allocated to on-demand treatment, the treatment period with nonacog beta pegol was 28 weeks. After completion of the NN7999-3747 study, all patients had the possibility to switch to the NN7999-3775 extension study (as was the case for a further study NN7999-3773) and continue their respective treatment with nonacog beta pegol for an additional period of at least 12 months. In the extension study, the patients had the possibility to switch between the treatment arms.

Since all patients in the NN7999-3747 study were treated with nonacog beta pegol and there was no control arm for conducting an adjusted indirect comparison, the company tried to derive an added benefit from different analyses of individual arms of its studies NN7999-3747 and NN7999-3775:

- Before-after comparison: The company compared the treatment effect of a prophylactic study treatment with nonacog beta pegol versus prophylactic treatment with recombinant or human plasma-derived coagulation factor IV products received before the start of the study. For this purpose, the company presented analyses on several outcomes for patients who had received prophylactic treatment both before the start of the study and during the study. To show transferability to the German health care context, it presented additional analyses from this subpopulation for patients from Europe (EU population).
- "Improvement not yet achieved in the actual health care setting": The company described considering the "absolute extent of the effect" (of individual study arms on nonacog beta pegol) as measure for the added benefit. According to the company, this approach was particularly suitable for outcomes in which nonacog beta pegol achieved an "improvement not yet achieved in the actual health care setting" in the sense of a "dramatic" effect. For this purpose, the company presented analyses on patients of the approval-compliant

prophylactic treatment arm with nonacog beta pegol from the two approval studies mentioned besides the analyses mentioned above.

However, no added benefit of nonacog beta pegol could be derived from the analyses presented by the company because these were inadequate with regard to content and, in addition, were based on an incomplete study pool.

For its before-after comparison, the company used results on patients who had received approval-compliant long-term prevention (40 IU per kg body weight once weekly [7]) in its studies NN7999-3747 and NN7999-3775 and who also had received prophylactic treatment in the framework of their individual care already before the start of the study. However, it cannot be inferred from the study documents on NN7999-3747 and NN7999-3775 that the patients considered by the company had received adequate prophylactic treatment with recombinant or human plasma-derived coagulation factor IX products before the start of the study (see Table 9 in Appendix A of the full dossier assessment). In the framework of an approval-compliant long-term prevention, the factor products would have had to be applied at intervals of 3 to 4 days [8,9]. Exact information was missing for most patients so that an adequate frequency of application could be derived from this information only for a small proportion of the patients.

However, the treatment conducted under study conditions cannot be compared to prophylactic treatment outside the study situation. This is irrespective of the question whether the pretreatment was provided adequately. This can be illustrated, for example, with results from the Valentino 2014 study [10], which was identified in a systematic literature search on the topic of treatment of haemophilia patients [11]. In Valentino 2014, a patient population comparable to the patient population in the studies NN7999-3747 and NN7999-3775 received approval-compliant prophylaxis with the recombinant drug nonacog alfa. The observed annual bleeding rate was of a similar magnitude as the bleeding rate under approval-compliant prophylaxis with nonacog beta pegol (see Figure 1 in Appendix B of the full dossier assessment). Studies with other recombinant coagulation factor IX products with prolonged half-lives, e.g. study 2004 [12] on albutrepenonacog alfa, also reported similar annual bleeding rates under study conditions (see Figure 1 in Appendix B of the full dossier assessment). Hence not only the company's before-after comparison was not informative, but the company's approach of showing "improvements not yet achieved in the actual health care setting" for individual outcomes was also refuted.

In addition, the company conducted no information retrieval for the ACT. Hence the company's information retrieval on further investigations was incomplete with regard to content and unsuitable for a comparison between nonacog beta pegol and the comparator therapy.

Supplementary notes

In its dossier, the company did not investigate the on-demand therapeutic situation with nonacog beta pegol, which is also part of the therapeutic indication, however.

In addition, the dossier presented by the company has various inconsistencies. This particularly concerns the company's explanations on the choice of the ACT (see Section 2.7.1 of the full dossier assessment) and a formulation of the inclusion and exclusion criteria for identification of the studies that deviated from the research question (see Section 2.7.2.1 of the full dossier assessment). In addition, the information provided by the company on the study pool was inconsistent (see Section 2.7.2.3.2 of the full dossier assessment).

2.4 Results on added benefit

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

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of nonacog beta pegol in comparison with the ACT is shown in Table 5.

Table 5: Nonacog beta pegol – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency)	**Recombinant or human plasma-derived coagulation factor IX products**	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 the approach of the company, which derived a hint of a non-quantifiable added benefit of nonacog beta pegol with "at least considerable" extent.

The G-BA decides on the added benefit.

2.6 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/en/projects-results/projects/drug-assessment/a17-57-nonacog-beta-pegol-haemophilia-b-benefit-assessment-according-to-35a-social-code-book-v.8400.html.