IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Simoctocog alfa – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 February 2015). 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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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 simoctocog 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 30 October 2014.

Research question

The aim of the present report was to assess the added benefit of simoctocog 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

The company chose the recombinant coagulation factor octocog alfa as one of the options specified as ACT by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company. The minimum study duration for prophylactic treatment is 6 months.

Results

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

Direct comparison

The company identified 2 randomized controlled trials (RCTs) that it considered to be relevant and in which simoctocog alfa was compared with octocog alfa in pretreated patients with severe haemophilia A (Part 1 of each of the studies GENA-01 and GENA-09). The RCT parts of both studies were conducted in a randomized, unblinded cross-over design. The primary objective of these parts was to determine the pharmacokinetic profile. The patients initially received a single dose of simoctocog alfa or octocog alfa and eventually, after a wash-out phase, a second single dose of the respective other drug.

Both pharmacokinetic studies were unsuitable for the assessment of the added benefit of simoctocog alfa in comparison with the ACT specified by the G-BA because of the short study duration (single administration).

Hence no relevant direct comparative studies were available for the assessment of the added benefit of simoctocog alfa versus the ACT. Incidentally, the company also derived no advantage of simoctocog alfa in comparison with octocog alfa from these 2 studies.

Further investigations

The company identified 5 one-arm studies for the drug to be assessed. All 5 studies investigated the efficacy and safety of simoctocog alfa in pretreated patients with severe haemophilia A of different age groups and in different treatment regimens (prophylaxis or on-demand treatment). The study duration of 4 of the studies was at least 6 months; the fifth study was an extension study of the GENA-09 study described above, which was completed at a fixed date.

For the derivation of an added benefit, the company presented a descriptive comparison of the results of these simoctocog alfa studies with results from approval studies of the ACT octocog alfa. The company exclusively used Summaries of Product Characteristics (SPCs) and publicly available documents from regulatory authorities. However, the company conducted no systematic search to identify studies with octocog alfa. This approach cannot ensure the completeness of the study pool for the ACT.

Hence the documents presented by the company as further investigations were unsuitable to draw conclusions on the added benefit of simoctocog alfa in comparison with octocog alfa.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

[4] 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), see [1]. 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), see [2].

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

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment and prophylaxis of bleeding in children and adults with haemophilia A (congenital factor VIII deficiency)	**Recombinant**[b] or human plasma-derived **coagulation factor VIII 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**. b: Choice on the basis of the company's information in the dossier: octocog alfa. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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 simoctocog 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

The company chose the recombinant coagulation factor octocog alfa as one of the options specified as ACT by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company. The minimum study duration for prophylactic treatment is 6 months.

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 simoctocog alfa (studies completed up to 16 September 2014)
- bibliographical literature search on simoctocog alfa (last search on 8 October 2014)
- search in trial registries for studies on simoctocog alfa (last search on 16 September 2014)

To check the completeness of the study pool:

- search in trial registries for studies on simoctocog alfa (last search on 5 December 2014)

No additional relevant study was identified from the check.

However, the data presented by the company were unsuitable to derive conclusions on the added benefit of simoctocog alfa in patients with haemophilia A.

Direct comparison

The company identified 2 RCTs that it considered to be relevant and in which simoctocog alfa was compared with octocog alfa in pretreated patients with severe haemophilia A (Part 1 of each of the studies GENA-01 [3,4] and GENA-09 [5]). The RCT parts of both studies were conducted in a randomized, unblinded cross-over design. The primary objective of these parts was to determine the pharmacokinetic profile. The patients initially received a single dose of simoctocog alfa or octocog alfa and eventually, after a wash-out phase, a second single dose of the respective other drug. After administration of the coagulation factor, factor VIII levels were determined at defined time points over a period of 48 hours.

Both pharmacokinetic studies were unsuitable for the assessment of the added benefit of simoctocog alfa in comparison with the ACT specified by the G-BA because of the short study duration (single administration). The European Medicines Agency (EMA)'s guidelines on the planning and conduct of approval studies for recombinant and human plasma-derived coagulation factor products specify a minimum study duration of 6 months with the investigational product in long-term prophylaxis [6]. Since simoctocog alfa is approved for the prophylaxis of bleeding and therefore for long-term use, a minimum study duration of 6 months is required to be able to assess an effect of increased blood coagulation and a potential effect on patient-relevant outcomes (e.g. number of bleeding events) with certainty. In cases where on-demand treatment or efficacy in acute bleeding is investigated, a minimum study duration of 50 exposure days may be used alternatively, according to EMA [6]. However, this was not the case in the available studies (prophylactic administration to investigate pharmacokinetics) and, moreover, the minimum exposure would not have been fulfilled for this treatment situation either.

Hence no relevant direct comparative studies were available for the assessment of the added benefit of simoctocog alfa versus the ACT. Incidentally, the company also derived no advantage of simoctocog alfa in comparison with octocog alfa from these 2 studies.

Further investigations

The company identified 5 one-arm studies for the drug to be assessed: Part 2 of the studies GENA-01 [3] and GENA-09 [5], and the studies GENA-03 [7], GENA-04 [8] and GENA-08 [9,10]. All 5 studies investigated the efficacy and safety of simoctocog alfa in pretreated patients with severe haemophilia A of different age groups and in different treatment regimens (prophylaxis or on-demand treatment). The study duration was at least 6 months in the studies GENA-01, GENA-09, GENA-03 and GENA-08. GENA-04 was an extension study of the GENA-09 study, which was completed at a fixed date.

For the derivation of an added benefit, the company presented a descriptive comparison of the results of these simoctocog alfa studies with results from approval studies of the ACT octocog alfa in Module 4 (Section 4.3.2.3.5). The company exclusively used SPCs and publicly available documents from regulatory authorities. The company conducted no systematic information retrieval to identify studies with octocog alfa, which is required according to the dossier templates. This approach cannot ensure the completeness of the study pool for the ACT. A simplified search additionally identified the study Valentino 2012 [11], for example, in which different treatment regimens of octocog alfa (Advate) were investigated over a total time period of 18 months (see Section 2.7.2.3.1 of the full dossier assessment). Hence the documents presented by the company as further investigations were unsuitable to draw conclusions on the added benefit of simoctocog alfa in comparison with octocog alfa.

2.4 Results on added benefit

The company presented no relevant data for the assessment of the added benefit of simoctocog alfa in its dossier. Hence the added benefit of simoctocog 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 simoctocog alfa in comparison with the ACT is shown in Table 3.

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

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment and prophylaxis of bleeding in children and adults with haemophilia A (congenital factor VIII deficiency)	**Recombinant**[b] or human plasma-derived **coagulation factor VIII 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**. b: Choice on the basis of the company's information in the dossier: octocog alfa. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This deviates from the company's approach, which derived a hint of a non-quantifiable added benefit of simoctocog alfa, the extent of which it claimed to be "considerable", however.

The G-BA decides on the added benefit.

2.6 List of included studies

The information usually provided here is not applicable as the studies included by the company were unsuitable for the assessment of the added benefit of simoctocog alfa versus the ACT specified by the G-BA for the reasons stated above.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-41-simoctocog-alfa-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6490.html.