Evinacumab (homozygous familial hypercholesterolaemia, children 5 to 11 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 2 of the dossier assessment *Evinacumab (homozygote familiäre Hypercholesterinämie, Kinder 5 bis 11 Jahre) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HoFH	homozygous familial hypercholesterolemia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL	low-density lipoprotein
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 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 evinacumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 10 January 2024.

Research question

The aim of this report is to assess the added benefit of evinacumab as an adjuvant therapy to diet and other lipid-lowering therapies compared to the appropriate comparator therapy (ACT) in children aged 5 to 11 years with homozygous familial hypercholesterolemia (HoFH) in whom dietary and drug options for lipid lowering have been exhausted.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of evinacumab

Therapeutic indication	**ACT**[a]
Children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] (10 years and older) and/or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment

a. Presented is the respective ACT specified by the G-BA.
b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
c. The G-BA guideline on examination and treatment methods provided under statutory health insurance must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

In Module 3 B, the company deviates from the formulation of the G-BA's ACT and specifies a maximum tolerated lipid-lowering therapy of physician's choice as the ACT for children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted, taking into account statins, ezetimibe, evolocumab (for children aged 10 years and older) and low-density lipoprotein (LDL) apheresis. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit assessment – neither versus a comparator therapy specified by the company nor versus the ACT 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. Studies with a minimum duration of 12 months were used for the derivation of the added benefit.

Results

No RCT directly comparing evinacumab to the ACT was identified through the information retrieval.

As the company also did not identify any RCT for the direct comparison of evinacumab in comparison with the ACT, it conducted an information retrieval for further investigations on evinacumab. In this information retrieval, the company identified the single-arm R1500-CL-17100 study and used this study to derive the added benefit. Data from 20 children aged 5 to 11 years with HoFH, who were treated with evinacumab, were included in this study.

This approach is not appropriate. The analyses of the single-arm R1500-CL-17100 study presented by the company do not enable a comparison of evinacumab versus the ACT. Thus, the R1500-CL-17100 study is not suitable for assessing the added benefit of evinacumab.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of evinacumab 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

Table 3 shows a summary of the probability and extent of added benefit of evinacumab.

Table 3: Evinacumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children with HoFH aged 5 to 11 years in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] (10 years and older) and/or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
c. The G-BA guideline on examination and treatment methods provided under statutory health insurance must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of evinacumab as an adjuvant therapy to diet and other lipid-lowering therapies compared to the appropriate comparator therapy (ACT) in children aged 5 to 11 years with homozygous familial hypercholesterolemia (HoFH) in whom dietary and drug options for lipid lowering have been exhausted.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of evinacumab

Therapeutic indication	**ACT**[a]
Children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] (10 years and older) and/or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment
a. Presented is the respective ACT specified by the G-BA. b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [1] must be observed. c. The G-BA guideline on examination and treatment methods provided under statutory health insurance [2] must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein	

On receipt of the dossier, the G-BA adjusted the ACT on 06 February 2024 in as presented in Table 4 [3]. Following this adjustment, the originally defined research question 1 is no longer required: : Children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have not been exhausted. According to the G-BA's adjustment (which refers to the company's reasoning according to Module 3 B), this patient population is not part of the target population of evinacumab and thus not part of this benefit assessment. The original research question 2 – Children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted – remains unaffected by the adjustment. The present benefit assessment is conducted according to the adjusted ACT for children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted.

In Module 3 B, the company deviates from the formulation of the G-BA's ACT and specifies a maximum tolerated lipid-lowering therapy of physician's choice as the ACT for children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted, taking into account statins, ezetimibe, evolocumab (for children aged 10 years and older) and low-density lipoprotein (LDL) apheresis. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company’s deviation from the ACT specified by the G-BA will not be further commented on below because the company did not present any suitable data for the benefit assessment – neither compared to a

comparator therapy designated by the company nor compared to the ACT specified by the G-BA (see Section I 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 12 months were used for the derivation of the added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 24 weeks. This deviation is of no consequence for the present assessment, as the company did not present any data on the comparison of evinacumab with the ACT (for reasons, see Chapter I 3).

I 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 evinacumab (status: 15 November 2023)
- bibliographical literature search on evinacumab (last search on 15 November 2023)
- search in trial registries/trial results databases for studies on evinacumab (last search on 13 November 2023)
- search on the G-BA website for evinacumab (last search on 14 November 2023)
- bibliographical literature search on the ACT (last search on 15 November 2023)
- search in trial registries/trial results databases for studies on the ACT (last search on 13 November 2023)
- search on the G-BA website for the ACT (last search on 14 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on evinacumab (last search on 24 January 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, no RCT on the direct comparison of evinacumab versus the ACT was identified from the check.

As the company did not identify any RCT for the direct comparison of evinacumab in comparison with the ACT, it conducted an information retrieval for further investigations on evinacumab. In this information retrieval, the company identified the single-arm R1500-CL-17100 study [4] and used this study to derive the added benefit. For the comparator part, the company only carried out information retrieval for RTCs and did not consider any single-armed studies. In doing so, it stated that it did not identify any studies with the ACT. The completeness of the study pool for further investigations was not checked.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of evinacumab in comparison with the ACT. This is justified below.

R1500-CL-17100 study

The R1500-CL-17100 study is a single-arm, open-label study. It included children aged 5 to 11 years with HoFH. The diagnosis of HoFH was based on genetic or clinical criteria. For screening, patients had to have a LDL cholesterol (C) value > 130 mg/dL. All patients were required to

maintain their training routine and were regularly questioned about their dietary compliance. The study had 3 parts:

- Part A consisted of a ≤ 8-week run-in phase, 1 to 2 weeks of screening, and a single treatment with evinacumab (15 mg/kg body weight intravenously [IV]) followed by a 16-week observation period. The primary objective of this study part was to investigate the pharmacokinetics of evinacumab in paediatric patients with HoFH. Subsequently, the patients could either participate in Part C of the study and continue to be treated or were followed up for 8 weeks afterwards.
- Part B consisted of a ≤ 8-week run-in phase, 1 to 2 weeks of screening, and an open-label treatment phase with evinacumab for 24 weeks. The primary outcome of this study part was the change in LDL-C value between baseline and week 24. Subsequently, the patients could either participate in Part C of the study and continue to be treated or were followed up for 20 weeks afterwards.
- In Part C, patients from Part A and Part B could continue to be treated with evinacumab for 48 weeks. Subsequently, they were followed up for 24 weeks.

In Part A of the study, data on the pharmacokinetics and pharmacodynamics of evinacumab were recorded to determine the appropriate dose for parts B and C of the study. The analysis of this data did not lead to any change in the dosage, so patients in Part B and Part C were treated without change with 15 mg/kg body weight of evinacumab IV every 4 weeks.

The included patients had to be on a maximum tolerated lipid-lowering therapy at the time of study inclusion. This background therapy had to remain unchanged for 4 weeks before screening or 8 weeks for treatment with Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors (run-in phase). No adjustments to background therapy were allowed during the study. Patients who underwent LDL apheresis could be included if it was performed according to a fixed regimen (weekly or bi-weekly) for ≥ 8 weeks prior to screening, and if it was expected that the treatment plan would remain unchanged throughout the treatment period. The frequency of LDL apheresis was to remain unchanged during the course of the study; only in Part C of the study could the frequency be reduced at the discretion of the investigator.

In Module 4 B, the company presented pooled data of parts B and C, of the study, which comprised a total of 20 patients. Of these, 6 patients received treatment in Part A of the study and subsequently switched to Part C of the study. 14 patients started the study in Part B and also subsequently switched to Part C of the study.

All patients included in the analyses were receiving lipid-lowering therapy at baseline and, according to the investigator, this was the maximum tolerated lipid-lowering therapy for all of them. 18 (90 %) patients were taking a statin and 10 (50 %) patients were taking high-dose statins. At baseline, all patients were also receiving non-statin lipid-lowering therapy: 19 (95%) patients received ezetimibe and 2 (10%) patients were treated with lomitapide. No patients

were treated with PCSK9 inhibitors in the study. 12 (60%) of the patients underwent LDL apheresis.

R1500-CL-17100 study unsuitable for the benefit assessment

The company presented analyses of R1500-CL-17100 study for the benefit assessment. R1500-CL-17100 is a single-arm study and thus does not enable a direct comparison of evinacumab versus the ACT. Thus, contrary to the company's assessment, the R1500-CL-17100 study is not suitable for assessing the added benefit of evinacumab.

I 4 Results on added benefit

There are no suitable data available for the assessment of the added benefit of evinacumab as an adjuvant therapy to diet and other lipid-lowering therapies compared to the ACT in children aged 5 to 11 years with HoFH in whom dietary and drug options for lipid lowering have been exhausted. There is no hint of an added benefit of evinacumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

The result of the assessment of the added benefit of evinacumab in comparison with the ACT is summarized in Table 5.

Table 5: Evinacumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children with HoFH aged 5 to 11 years in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[b] (10 years and older) and/or LDL apheresis[c] (as "last resort" in refractory disease) possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [1] must be observed.
c. The G-BA guideline on examination and treatment methods provided under statutory health insurance [2] must be taken into account with regard to performing outpatient apheresis as extracorporeal haemotherapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HoFH: homozygous familial hypercholesterolaemia; LDL: low density lipoprotein

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

The G-BA decides on the added benefit.

[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 [5,6].

I 6 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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