Alirocumab (heterozygous familial hypercholesterolaemia in paediatric patients 8 years of age and older)

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

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

No patients or their families were involved in the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Ulrike Mikulić
- Lisa Junge
- Claudia Kapp
- Corinna Kiefer
- Petra Kohlepp
- Daniela Preukschat
- Min Ripoll
- Kathrin Wohlhöfner

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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
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HeFH	heterozygous familial hypercholesterolaemia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDL	low-density lipoprotein
LDL-C	LDL cholesterol
RCT	randomized controlled trial
SAE	serious adverse event
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) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug alirocumab. 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 14 December 2023.

Research question

The aim of the present report was to assess the added benefit of alirocumab as an adjunct to dietary therapy and, if applicable, a statin and/or other lipid-lowering therapies compared with the appropriate comparator therapy (ACT) in paediatric patients 8 years of age and older and adolescents with heterozygous familial hypercholesterolaemia (HeFH).

The research questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of alirocumab

Research question	Therapeutic indication	ACT[a]
1	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have not been exhausted	Maximum tolerated drug treatment according to physician's choice, selecting from statins, cholesterol absorption inhibitors, and anion exchangers
2	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[c] (10 years and older) or LDL apheresis[d] (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment

a. Presented is the respective ACT specified by the G-BA.
b. Use of alirocumab in accordance with the approval as an adjunct to diet in conjunction with a statin or with a statin and other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated statin therapy or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.
c. The stipulations of Appendix III of the Pharmaceutical Directive must be observed.
d. 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; HeFH: heterozygous familial hypercholesterolaemia; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

For research question 1, children 8 years of age and older and adolescents with HeFH, in whom dietary and drug options for lowering lipids have not been exhausted, the company followed the G-BA's specifications with regard to ACT. For research question 2, children 8 years of age and older and adolescents with HeFH, in whom dietary and drug options for lipid lowering

have been exhausted, the company deviated from the G-BA's specifications with regard to ACT. It only named low-density lipoprotein (LDL) apheresis, but not evolocumab, as an ACT for this research question.

The company's deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA. For both research questions, the present benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 1 year are used for the derivation of the added benefit.

Results

No relevant study was identified for assessing the added benefit of alirocumab in comparison with the ACT For either research question. The EFC14643 study presented by the company only as a supplement is not suitable for the assessment of the added benefit of alirocumab.

EFC14643 is a randomized, multicentre study comparing alirocumab with placebo with double-blind treatment over a period of 24 weeks, followed by an 80-week open-label treatment phase during which all patients received alirocumab. Children and adolescents aged between 8 and 17 years with diagnosed HeFH that was inadequately controlled despite statin treatment with or without additional lipid-modifying therapy or in the case of statin intolerance despite treatment with other (non-statin-based) lipid-modifying therapies were included. A total of 8 patients (10%) in the Q4W cohort (treatment with alirocumab every 4 weeks in compliance with the marketing authorisation) had statin intolerance. 22 of the 71 patients treated with statins received the maximum tolerated statin dose (31%), with "regional practice or local guideline" given as the reason why treatment was not intensified in 47 patients. The lipid-modifying therapy existing at the time of study inclusion had to have been given at a stable dose for at least 4 weeks before the start of the study and was not allowed to be modified during the double-blind treatment phase. Evolocumab and LDL apheresis were not administered in the study.

The study does not allow for comparison with the ACT, as on the one hand the existing inadequate lipid-modifying therapy could not be adjusted and thus a maximum tolerated drug treatment according to physician's choice (corresponding to the ACT for research question 1) was not used. On the other hand, evolocumab and LDL apheresis were also not used in the study, so the study does not allow a comparison with the ACT according to research question 2. As the majority of patients did not receive an intensification of statin therapy due to regional

practice or local guidelines, it is also not ensured that the patients included received prior therapy with a maximum tolerated statin dose as per marketing authorization for alirocumab.

Regardless, the double-blind treatment duration of the study is only 24 weeks. Alirocumab serves as long-term treatment of a chronic disease with the primary goal of lowering LDL-C values to reduce cardiovascular risks. A longer controlled treatment phase is therefore necessary to assess the long-term effects of alirocumab on patient-relevant outcomes.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of alirocumab 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 5 shows a summary of probability and extent of the added benefit of alirocumab.

[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].

Table 3: Alirocumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have not been exhausted	Maximum tolerated drug treatment according to physician's choice, selecting from statins, cholesterol absorption inhibitors, and anion exchangers	Added benefit not proven
2	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[c] (10 years and older) or LDL apheresis[d] (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Use of alirocumab in accordance with the approval as an adjunct to diet in conjunction with a statin or with a statin and other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated statin therapy or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.
c. The stipulations of Appendix III of the Pharmaceutical Directive must be observed.
d. 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; HeFH: heterozygous familial hypercholesterolaemia; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report was to assess the added benefit of alirocumab as an adjunct to dietary therapy and, if applicable, a statin and/or other lipid-lowering therapies compared with the ACT in children 8 years of age and older and adolescents with HeFH.

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of alirocumab

Research question	Therapeutic indication	ACT[a]
1	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have not been exhausted	Maximum tolerated drug treatment according to physician's choice, selecting from statins, cholesterol absorption inhibitors, and anion exchangers
2	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[c] (10 years and older) or LDL apheresis[d] (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment

a. Presented is the respective ACT specified by the G-BA.
b. Use of alirocumab in accordance with the approval as an adjunct to diet in conjunction with a statin or with a statin and other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated statin therapy or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated [3].
c. The stipulations of Appendix III of the Pharmaceutical Directive [4] must be observed.
d. 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 [5].

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HeFH: heterozygous familial hypercholesterolaemia; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

For research question 1, children 8 years of age and older and adolescents with HeFH, in whom dietary and drug options for lowering lipids have not been exhausted, the company followed the G-BA's specifications with regard to ACT. For research question 2, children 8 years of age and older and adolescents with HeFH, in whom dietary and drug options for lipid lowering have been exhausted, the company deviated from the G-BA's specifications with regard to ACT. It only named LDL apheresis, but not evolocumab, as an ACT for this research question.

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. For both research questions, the present benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 1 year are used for the derivation of the added benefit. This deviates from inclusion criteria of the company, which specified a minimum study duration of 3 months.

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 list on alirocumab (status: 16 October 2023)
- bibliographical literature search on alirocumab (last search on 10 October 2023)
- search in trial registries/trial results databases for studies on alirocumab (last search on 16 October 2023)
- search on the G-BA website for alirocumab (last search on 16 October 2023)
- bibliographical literature search on the ACT (last search on 10 October 2023)
- search in trial registries/trial results databases for studies on the ACT (last search on 16 October 2023)
- search on the G-BA website for the ACT (last search on 16 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on alirocumab (last search on 21 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not reveal any relevant study for assessing the added benefit of alirocumab in comparison with the ACT for either of the 2 research questions. This concurs with the company's assessment. In Module 4 E, the company only presented supplementary results of the EFC14643 approval study [6]. In addition, the company conducted an information retrieval for an adjusted indirect comparison via the common comparator placebo, but did not present the results of the information retrieval. Instead, the company explained why, in its view, an indirect comparison for the assessment of added benefit based on the EFC14643 approval study was not possible. This is explained below. No check of completeness of the information retrieval on the ACT was conducted.

The EFC14643 study is a randomized multicentre study comparing alirocumab with placebo with double-blind treatment over a period of 24 weeks. This was followed by an 80-week open treatment phase during which all patients received alirocumab. Children and adolescents aged between 8 and 17 years with diagnosed HeFH that was inadequately controlled despite statin treatment with or without additional lipid-modifying therapy or in the case of statin intolerance despite treatment with other (non-statin-based) lipid-modifying therapies were included. (LDL cholesterol [LDL-C] level ≥ 130 mg/dL at the time of screening). The optimal statin dose was defined as the stable daily dose recommended on the basis of regional or national guidelines or as the stable maximum tolerated daily dose. Statin intolerance was

defined as the inability to tolerate at least 2 statins (one statin at the lowest daily starting dose and another statin at any dose) due to musculoskeletal symptoms. The study medication was administered every 2 or every 4 weeks (Q2W and Q4W cohorts), with the 4-weekly administration corresponding to the Summary of Product Characteristics for alirocumab [3]. A total of 8 patients (10%) in the Q4W cohort had statin intolerance. 22 of the 71 patients treated with statins received the maximum tolerated statin dose (31%), with "regional practice or local guideline" given as the reason why treatment was not intensified in 47 patients. The lipid-modifying therapy existing at the time of study inclusion had to have been given at a stable dose for at least 4 weeks before the start of the study and was not allowed to be modified during the double-blind treatment phase. Dose adjustments, initiation of new treatment or discontinuation of an existing lipid-modifying therapy were not permitted. Evolocumab and LDL apheresis (corresponding to the ACT for research question 2) were not administered in the study.

The company excluded the study on the grounds that it did not allow a comparison with the ACT, neither for research question 1 nor for research question 2. The company also ruled out the possibility of an indirect comparison. For research question 1, the company justified this by stating that a maximum tolerated drug treatment according to physician's choice, taking into account statins, cholesterol absorption inhibitors and anion exchangers (ACT for research question 1), was already an inclusion criterion for all patients in study EFC14643. For research question 2, it argued that no data from RCTs with a paediatric population were available for LDL apheresis.

The study does not allow for comparison with the ACT, as on the one hand the existing inadequate lipid-modifying therapy could not be adjusted and thus a maximum tolerated drug treatment according to physician's choice (corresponding to the appropriate comparator therapy for research question 1) was not used. On the other hand, evolocumab and LDL apheresis were also not used in the study, so the study does not allow a comparison with the ACT according to research question 2.

Is not immediately apparent from the inclusion criteria that a maximum tolerated drug treatment according to physician's choice, taking into account statins, cholesterol absorption inhibitors, and anion exchangers, is an inclusion criterion of the study EFC14643. It merely states that patients should have received an optimal statin dose with or without other lipid-modifying therapy or, in the case of statin intolerance, other (non-statin-based) lipid-modifying therapies as prior therapy and how an optimal statin dose is defined (see above). As the majority of patients did not receive an intensification of statin therapy due to regional practice or local guidelines, it is also not ensured that the patients included received prior therapy with a maximum tolerated statin dose as per marketing authorization for alirocumab. In total, only 4 out of 27 patients in the comparator arm received the cholesterol absorption

inhibitor ezetimibe [7]. Anion exchangers were not used at all during the course of the study. It is unclear whether therapy with cholesterol absorption inhibitors and anion exchangers had already been exhausted in patients before the start of the study.

Regardless, the double-blind treatment duration of the study is only 24 weeks. Alirocumab serves as long-term treatment of a chronic disease with the primary goal of lowering LDL-C values to reduce cardiovascular risks. Assessing the long-term effects of alirocumab on patient-relevant outcomes therefore requires a longer controlled treatment phase than 3 months as defined in the company's inclusion criteria or 24 weeks as used in the study EFC14643.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of alirocumab as an adjunct to dietary therapy and, if applicable, a statin and/or other lipid-lowering therapies compared with the ACT in children 8 years of age and older and adolescents with HeFH. There is no hint of added benefit of alirocumab in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Alirocumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have not been exhausted	Maximum tolerated drug treatment according to physician's choice, selecting from statins, cholesterol absorption inhibitors, and anion exchangers	Added benefit not proven
2	Children 8 years of age and older and adolescents with HeFH[b] in whom dietary and drug options for lipid lowering have been exhausted	Evolocumab[c] (10 years and older) or LDL apheresis[d] (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Use of alirocumab in accordance with the approval as an adjunct to diet in conjunction with a statin or with a statin and other lipid-lowering therapies in patients who are unable to reach LDL-C goals with the maximum tolerated statin therapy or as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated [3].
c. The stipulations of Appendix III of the Pharmaceutical Directive [4] must be observed.
d. 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 [5].

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HeFH: heterozygous familial hypercholesterolaemia; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-136.html.