IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Alirocumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 February 2016). 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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
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 alirocumab. 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 2 November 2015.

Research question

The aim of the present report was to assess the added benefit of alirocumab in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet and, if applicable, other lipid-lowering therapies:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low-density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a statin
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

The G-BA distinguished between different patient groups in its specification of the ACT. This resulted in 3 research questions for the assessment. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of alirocumab

Research question	Patient population	ACT[a]
A	Patients for whom statins are a treatment option[b,c]	Maximum tolerated drug and dietary treatment to reduce lipid levels
B	Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[c]	Other lipid-lowering drugs (**fibrates or anion exchangers or cholesterol resorption inhibitors**) as monotherapy
C	Patients in whom drug and dietary lipid-lowering options have been exhausted	LDL apheresis (as "last resort" in refractory disease)[d]

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: In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin.
c: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive.
d: Documented maximum tolerated drug and dietary treatment to reduce lipid for at least 12 months is the general prerequisite for LDL apheresis. Concomitant lipid-lowering drug and dietary treatment is possible and should be appropriately recorded.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

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

Results

Research question A: patients for whom statins are a treatment option

The company identified 8 studies that it used for the derivation of the added benefit, and one further study, the results of which it only presented as additional information. All 9 studies were not relevant for the present benefit assessment.

The 8 studies included by the company were the RCTs FH I, FH II, HIGH FH, COMBO I, COMBO II, LONG TERM, OPTIONS I and OPTIONS II.

The company cited the CHOICE I study as part of the relevant study pool for research question A, but presented its results only as additional information.

The designs of all these studies contained one or several aspects opposed to an inclusion for the benefit assessment because they did not comply with the inclusion criteria for the present research question. These can be allocated to 3 categories:

- wrong population (patients had not received pretreatment with the maximum tolerated dose of a statin) in 7 of the 9 studies
- wrong comparator therapy (comparator did not comply with the appropriate comparator therapy [ACT]) in all studies
- study duration too short (< 1 year) in 2 of the 9 studies

Hence no relevant data for the assessment of the added benefit of alirocumab in comparison with the ACT were available for research question A. Overall, there was no hint of an added benefit of alirocumab in comparison with the ACT; an added benefit is therefore not proven.

Research question B

The company identified 2 studies it included in the benefit assessment. However, it only used the results of the study ALTERNATIVE for the assessment of the added benefit. The company cited the CHOICE II study as part of the relevant study pool, but presented the results only as additional information.

Both studies identified by the company were not relevant for the present benefit assessment.

The ALTERNATIVE study was a double-blind RCT, in which patients with statin intolerance and moderate to very high cardiovascular risk were included. The patients received either alirocumab, or ezetimibe, or low-dose atorvastatin in addition to diet and lipid-lowering basic therapy (without statins or ezetimibe).

The definition of "statin intolerance" was obviously unsuitable in the ALTERNATIVE study because some of the patients were allocated to treatment with a statin. In addition, the rate of discontinuations due to adverse events in the study arm with administration of atorvastatin concurred with the one in the ezetimibe arm (about 25% in each case) and was therefore not higher than in patients with statin-free treatment. Furthermore, the study duration of 24 weeks was notably below the required minimum duration of 1 year.

The CHOICE II study was a double-blind RCT in which 2 dose regimens of alirocumab were compared with placebo. Only patients were included who were not treated with statins, but, if applicable, with other lipid-lowering drugs. The patients had to have a moderate to very high cardiovascular risk. Hence only the subpopulation of patients with statin intolerance and high cardiovascular risk fulfilled the inclusion criteria for research question B. Again, the ACT specified by the G-BA was only used for some of the patients. The company presented no data for this subpopulation. In addition, the treatment duration of the study was 24 weeks and was therefore not long enough for the present benefit assessment.

Hence no relevant data for the assessment of the added benefit of alirocumab in comparison with the ACT were available for research question B. Overall, there was no hint of an added benefit of alirocumab in comparison with the ACT; an added benefit is therefore not proven.

Research question C

The company identified one study relevant from the company's point of view. The ESCAPE study was a double-blind RCT, in which adult patients with heterozygous familial hypercholesterolaemia were included who had regular LDL apheresis (every 1 or 2 weeks). Alirocumab + apheresis was compared with placebo + apheresis in the study. According to the company, the study was not yet completed at the time point of the submission of the dossier and there were no intermediate results yet. The company included the ESCAPE study as relevant in the benefit assessment, but presented no results for any of the outcomes. The study could therefore not be used for the present benefit assessment.

Furthermore, the treatment duration in the ESCAPE study was limited to 18 weeks; together with a follow-up phase of another 8 weeks, this resulted in a total study duration of notably less than one year. The study would therefore not be relevant for the benefit assessment even if results were available.

Hence no relevant data for the assessment of the added benefit of alirocumab in comparison with the ACT were available for research question C. Overall, there was no hint of an added benefit of alirocumab in comparison with the ACT; an added benefit is therefore not proven.

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 alirocumab versus the ACT are assessed as follows:

An added benefit of alirocumab is not proven for any of the 3 research questions because no relevant studies were available in each case.

Table 3 presents a summary of the extent and probability of the added benefit of alirocumab.

Table 3: Alirocumab – extent and probability of added benefit

Research question		**ACT**	**Extent and probability of added benefit**
A	Patients for whom statins are a treatment option[a, b]	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
B	Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[b]	Other lipid-lowering drugs (**fibrates or anion exchangers or cholesterol resorption inhibitors**) as monotherapy	Added benefit not proven
C	Patients in whom drug and dietary lipid-lowering options have been exhausted	LDL apheresis (as "last resort" in refractory disease)[c]	Added benefit not proven

a: In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive.
c: Documented maximum tolerated drug and dietary treatment to reduce lipid for at least 12 months is the general prerequisite for LDL apheresis. Concomitant lipid-lowering drug and dietary treatment is possible and should be appropriately recorded.
ACT: appropriate comparator therapy; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

The G-BA decides on the added benefit.

[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). 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). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of alirocumab in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet and, if applicable, other lipid-lowering therapies:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

The G-BA distinguished between different patient groups in its specification of the ACT. This resulted in 3 research questions for the assessment. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of alirocumab

Research question	**Patient population**	**ACT**[a]
A	Patients for whom statins are a treatment option[b, c]	Maximum tolerated drug and dietary treatment to reduce lipid levels
B	Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[c]	Other lipid-lowering drugs (**fibrates or anion exchangers or cholesterol resorption inhibitors**) as monotherapy
C	Patients in whom drug and dietary lipid-lowering options have been exhausted	LDL apheresis (as "last resort" in refractory disease)[d]

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: In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin.
c: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive [3].
d: Documented maximum tolerated drug and dietary treatment to reduce lipid for at least 12 months is the general prerequisite for LDL apheresis. Concomitant lipid-lowering drug and dietary treatment is possible and should be appropriately recorded.

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

According to Appendix III of the Pharmaceutical Directive, patients with existing vascular condition (coronary heart disease, cerebrovascular manifestation, peripheral arterial occlusive disease) or at high cardiovascular risk (over 20% event rate/10 years based on the available risk calculators) are exempt from the limitations of prescription of lipid-lowering drugs requiring prescription [3].

According to Appendix I of the G-BA Directive on Examination and Treatment Methods in Contracted Doctor Care, LDL apheresis in hypercholesterolaemia can only be conducted in patients with familial hypercholesterolaemia of the homozygous kind (not applicable here) or

in patients with severe hypercholesterolaemia in whom, generally, LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months [4].

The G-BA specified monotherapy with other lipid-lowering drugs (fibrates or anion exchangers or cholesterol resorption inhibitors) as ACT for research question B. Deviating from the G-BA, the company argued that other lipid-lowering drugs (fibrates or anion exchangers or cholesterol resorption inhibitors) are an option as ACT not only as monotherapy, but also as combination therapy (see Section 2.7.1 of the full dossier assessment). However, this had no consequence for the present benefit assessment because no relevant studies were available for research question B (see Section 2.4.1).

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum duration of 1 year were used for the derivation of the added benefit. This deviates from the company's approach, which, depending on the research question, included studies with a minimum duration of 3 months (research question C) or 6 months (research questions A and B).

2.3 Research question A: patients for whom statins are a treatment option

2.3.1 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: 6 October 2015)
- bibliographical literature search on alirocumab (last search on 14 October 2015)
- search in trial registries for studies on alirocumab (last search on 6 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on alirocumab (last search on 18 November 2015)

No relevant study was identified from the check.

Study pool of the company

With the steps of information retrieval mentioned, the company identified 8 studies that it used for the derivation of the added benefit, and one further study, the results of which it only presented as additional information. All 9 studies were not relevant for the present benefit assessment.

The 8 studies included by the company were the RCTs FH I [5], FH II [6], HIGH FH [7], COMBO I [8], COMBO II [9], LONG TERM [10], OPTIONS I [11] and OPTIONS II [12].

The company cited the CHOICE I study [13] as part of the relevant study pool for research question A, but presented its results only as additional information. The company justified this by claiming that the results of the study had not been published yet and that no final clinical study report was available yet, but only a short report with the key results. However, the company did not sufficiently justify that the results of the study could not be included in the benefit assessment on this basis (see Section 2.7.2.3.1 of the full dossier assessment).

The designs of all these studies contained one or several aspects opposed to an inclusion for the benefit assessment because they did not comply with the inclusion criteria for the present research question. These can be allocated to 3 categories:

- wrong population (patients had not received pretreatment with the maximum tolerated dose of a statin)
- wrong comparator therapy (comparator did not comply with the ACT)
- study duration too short

Table 5 shows the criteria in the respective studies due to which they were not included in the benefit assessment.

Table 5: Patients for whom statins are an option (research question A) – reasons for the lack of suitability of the studies included by the company

Study	Wrong population	Wrong comparator therapy	Study duration too short
FH I		●	
FH II		●	
HIGH FH	●	●	
COMBO I	●	●	
COMBO II	●	○[b]	
LONG TERM	●	●	
OPTIONS I	●	○[b]	●
OPTIONS II	●	○[b]	●
CHOICE I[a]	●	●	

a: The company initially included this study in its study pool, but presented it only as additional information in Appendix 4-G of Module 4 A.
b: In the studies COMBO II, OPTIONS I and OPTIONS II, treatment was intensified in the control groups, but a relevant proportion of the patients had not been pretreated with the maximum tolerated dose of a statin; intensification alone is no maximum tolerated lipid-lowering treatment in these cases.

Hereinafter, these aspects are described in more detail for the respective studies.

Prior therapy with maximum tolerated dose of a statin

Not reaching LDL-C goals with the maximum tolerated dose of a statin is a precondition for an approval-compliant use of alirocumab in patients for whom statins are an option [14]. It was therefore investigated whether this was the case for the patients in the studies included by the company.

In its studies (except OPTIONS I and II), the company defined dose criteria for the 3 statins rosuvastatin, atorvastatin and simvastatin, for which it assumed maximum tolerated treatment:

- Rosuvastatin 20 or 40 mg/day
- Atorvastatin 40 or 80 mg/day
- Simvastatin 80 mg/day; only patients who had received this dose for over one year were included
- Patients who could not receive the statin doses mentioned were to be treated with the dose considered adequate by the investigator. Accepted reasons for statin doses lower than the

ones mentioned included: adverse events at a higher dosage, advanced age, low body mass index (BMI), regional prescribing practice, local prescribing regulations, concomitant medications or disorders such as defective glucose tolerance or increased fasting plasma glucose levels. These reasons were mentioned and analysed in the case report forms so that the number of patients who had received a dose lower than the maximum dose defined above was evident in the study results.

This definition of a maximum tolerated dose of a statin was not followed. For atorvastatin in particular, the dose range cited by the company cannot be automatically regarded to be the maximum tolerated dosage because the approved maximum daily dose is 80 mg/day without limitation, according to the Summary of Product Characteristics (SPC) [15]. Hence 40 mg/day is only half the maximum dose. The company provided no information in its study documents whether patients with 40 mg/day atorvastatin had received this dose because they did not tolerate a higher dose or because they already fulfilled the company's definition of maximum tolerated treatment. It was therefore at least unclear whether these patients fulfilled the conditions for an approval-compliant use of alirocumab.

Moreover, some of the reasons accepted by the company cannot provide conclusions on tolerability.

This particularly applies to the following reasons: advanced age, low BMI and regional prescribing practice/local prescribing regulations. These can also not be inferred from the SPCs of atorvastatin, simvastatin and rosuvastatin [15-17].

This also applies to the COMBO II study, the only study included by the company that had both a duration of at least one year (104 weeks) and an active comparator (ezetimibe). The patients in the COMBO II study had been pretreated with a stable dose of statins and in the study received either alirocumab or ezetimibe in addition to this basic therapy. According to the company, the patients had not reached LDL-C goals with the maximum tolerated statin monotherapy. However, it was not clear from the available data that a sufficiently large proportion of patients had received the maximum tolerated dose of a statin before the start of the study at all. In the COMBO II study, 23.6% of the patients were treated with a daily dose of 40 mg/day atorvastatin at the start of the study. It was not described why these patients had not received the maximum dose of 80 mg/day. Another 16.5% of the patients had been pretreated with a low dose of a statin (less than 40 mg atorvastatin, 20 mg rosuvastatin or 80 mg simvastatin daily) due to regional features of the prescribing practice. In addition, there were patients who had received a lower dose of statins as basic therapy due to their age (1.5%), BMI (0.1%) or other reasons not further specified (1.8%) (double counting possible). Hence it was not proven for at least 40% of the patients in the COMBO II study that they had been pretreated with their maximum tolerated dose of a statin.

The situation was similar in the studies HIGH FH, CHOICE I, COMBO I and LONG TERM. The proportion of patients without proof that they had received their maximum tolerated statin

pretreatment was at least 24%, 31%, 35% and 43% in these studies. In the studies FH I and FH II, this proportion was below 20% in each case so that approval-compliant use of alirocumab was assumed for more than 80% of the included patients. These 2 studies were irrelevant for other reasons, however.

In contrast, only patients who had not reached the LDL-C goals on a not-maximum dose of statins were included in the studies OPTIONS I and OPTIONS II. This means that the patients in the OPTIONS I study had to be pretreated with 20 mg or 40 mg/day atorvastatin; and patients in the OPTIONS II study with 10 mg or 20 mg/day rosuvastatin. This corresponds to at most half the approved maximum dose in each case. Other statins than atorvastatin or rosuvastatin were not allowed in these studies. Hence both studies in their entirety did not investigate the population relevant for research question B.

Comparator therapy

In the treatment situation considered here, alirocumab was used in combination with diet and, if applicable, with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin. The ACT for this population was a maximum tolerated lipid-lowering drug and dietary treatment.

As described in the previous section, the patients in all studies had been pretreated with a stable statin therapy; it was not guaranteed in most studies that this had been the maximum tolerated dose of a statin. The patients in the studies FH I, FH II, HIGH FH, COMBO I, LONG TERM and CHOICE I received either alirocumab or placebo in addition to this stable basic medication. Since the dose of the lipid-lowering basic medication was not allowed to be adapted also in the placebo group, these studies ultimately constituted a comparison of alirocumab with placebo. It would have been necessary for an adequate comparison with a maximum tolerated drug and dietary treatment to further optimize the basic therapy for the individual patient at least in the placebo group, for example by adding another lipid-lowering drug, by adjusting the dose or by switching to a different lipid-lowering treatment. There was therefore no adequate comparator therapy in these studies.

Only patients treated with atorvastatin, simvastatin or rosuvastatin were included in the studies. Other statins were not allowed. Furthermore, the company's study documents showed that by far not all patients included had received other lipid-lowering drugs in addition to a statin. Their proportion was always below 70% in all the studies mentioned, sometimes also notably lower. Only 26% of the patients in the HIGH FH study, and only 30% of the patients in the LONG TERM study received further lipid-modifying drugs, for instance. It is not proven that a titration strategy (treat to target) based on an individual cholesterol level as threshold for a treatment indication with lipid-lowering drugs and on a therapeutic target level for LDL-C has advantages over a fixed standard dose of statins (fire and forget) regarding cardiovascular outcomes [18]. However, a titration strategy was used in the present studies because patients were included who had not reached LDL-C goals on their existing lipid-

lowering treatment and the reaching of target levels was aimed at in the intervention arms and the active control arms.

Research question A also represents this concept. Hence individually optimized treatment should have been possible also in the comparator arm because LDL threshold values were obviously exceeded with the existing basic therapy. Hence the studies mentioned above contained no comparison adequate for the research question.

The situation was somewhat different in the studies COMBO II, OPTIONS I and OPTIONS II.

In the control arm of the COMBO II study, prior therapy was escalated by the administration of ezetimibe. A relevant proportion of the patients in these studies had not been pretreated with the maximum tolerated dose of a statin, however, and further escalation of the statin dose was not allowed. Hence the combination with ezetimibe also constitutes no maximum tolerated drug and dietary treatment as required by the G-BA specification for this treatment situation. The comparator therapy in the COMBO II was therefore also not adequate.

Two strata of patients by dose of their prior statin therapy were included in the studies OPTIONS I and OPTIONS II: patients pretreated with 20 mg or 40 mg atorvastatin in the OPTIONS I study; patients pretreated with 10 mg or 20 mg rosuvastatin in the OPTIONS II study. These were randomized to the following treatments: alirocumab + basic statin therapy, ezetimibe + basic statin therapy, switching to rosuvastatin (OPTIONS I, only patients with 40 mg atorvastatin) or doubling of the ongoing statin dose (see Module 4 A of the dossier, pages 86 to 88).

For the arms “doubling of the ongoing statin dose”, this meant that patients pretreated with 40 mg atorvastatin or 20 mg rosuvastatin received a maximum statin dose according to the approval (80 mg atorvastatin or 40 mg rosuvastatin). Since these patients had not been pretreated with the maximum tolerated statin treatment it remained unclear also for them whether dose escalation to the maximum statin dose alone constitutes a maximum tolerated lipid-lowering treatment. The statements regarding the COMBO II study applies to the ezetimibe arms of the studies OPTIONS I and II.

In addition, this approach indicates again that the patient populations in these 2 studies did not correspond to the research question because doubling the statin dose is not possible after prior therapy with the maximum tolerated statin treatment.

Duration of study

Deviating from the company, a minimum study duration of 12 months was specified in the present benefit assessment because alirocumab is a long-term treatment for a chronic disease, which is mainly used for cardiovascular risk reduction (see Section 2.7.2.1 of the full dossier assessment). The studies OPTIONS I and OPTIONS II were not relevant for the present

benefit assessment because their study duration was only 32 weeks in total with a treatment duration of 24 weeks. Both studies were irrelevant for research question A of the benefit assessment already for other reasons (wrong population).

The other studies included by the company each had a duration of more than one year (treatment and follow-up).

2.3.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of the added benefit of alirocumab for research question A. This resulted in no hint of an added benefit of alirocumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of alirocumab as an adjunct to diet in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia for whom statins are a treatment option and who are unable to reach LDL-C goals with the maximum tolerated dose of a statin. Hence an added benefit of alirocumab is not proven for these patients.

This deviates from the company's approach, which derived proof of considerable added benefit of alirocumab on the basis of the data presented by the company. The added benefit derived by the company was mainly based on outcomes on the change of the LDL-C value during a period of 24 weeks. The company also used a selective and potentially event-driven post-hoc analysis of cardiovascular events from one of the studies it used for the derivation of the added benefit (see Section 2.7.2.8.2 of the full dossier assessment).

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question B: patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events

2.4.1 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: 6 October 2015)
- bibliographical literature search on alirocumab (last search on 14 October 2015)
- search in trial registries for studies on alirocumab (last search on 6 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on alirocumab (last search on 18 November 2015)

No relevant study was identified from the check.

Study pool of the company

From the steps of information retrieval mentioned, the company identified 2 studies it included in the benefit assessment. However, it only used the results of the study ALTERNATIVE [19] for the assessment of the added benefit. The company cited the CHOICE II study [20] as part of the relevant study pool, but presented the results only as additional information.

Both studies identified by the company were not relevant for research question B of the present benefit assessment.

Study ALTERNATIVE

The ALTERNATIVE study was a double-blind RCT, in which patients with statin intolerance and moderate to very high cardiovascular risk were included. The patients received either alirocumab, or ezetimibe, or low-dose atorvastatin in addition to diet and lipid-lowering basic therapy (without statins or ezetimibe). The treatment duration was 24 weeks, followed by an 8-week follow-up phase. Subsequently, patients could participate in an open-label one-arm extension study of 172 weeks with alirocumab treatment.

The definition of “statin intolerance” was obviously unsuitable in the ALTERNATIVE study because some of the patients were allocated to treatment with a statin. In addition, the rate of discontinuations due to adverse events in the study arm with administration of atorvastatin concurred with the one in the ezetimibe arm (about 25% in each case) and was therefore not higher than in patients with statin-free treatment.

Furthermore, the study duration of 24 weeks was notably below the required minimum duration of 1 year.

Study CHOICE II

The CHOICE II study was a double-blind RCT in which 2 dose regimens of alirocumab were compared with placebo. Only patients were included who were not treated with statins, but, if applicable, with other lipid-lowering drugs. The patients had to have a moderate to very high cardiovascular risk. Hence only the subpopulation of patients with statin intolerance and high cardiovascular risk fulfilled the inclusion criteria for the research question. The treatment duration was 24 weeks (total study duration: 35 weeks). This was followed by optional open-label continued treatment with alirocumab for 3 years, which, according to the company, is ongoing. The lipid-lowering basic medication was only adjusted in exceptional cases (ezetimibe or fenofibrate were allowed). Alirocumab or placebo were administered in addition to the ongoing lipid-lowering treatment. Since the G-BA specified a lipid-lowering drug in monotherapy as ACT, only those patients with statin intolerance were relevant for the benefit assessment who had also received a lipid-lowering drug in monotherapy (ezetimibe or fenofibrate) in addition to placebo. However, the company presented no data for this subpopulation.

Moreover, the duration of the randomized phase was notably below one year so that the minimum study duration defined for the present assessment was not fulfilled. The CHOICE II study was therefore not relevant for the present benefit assessment.

2.4.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of the added benefit of alirocumab for research question B. This resulted in no hint of an added benefit of alirocumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of alirocumab as an adjunct to diet in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia for whom statins are not a treatment option because of contraindications or intolerance. Hence an added benefit of alirocumab is not proven for these patients.

This deviates from the company’s approach, which derived an indication of considerable added benefit of alirocumab in comparison with ezetimibe on the basis of the data presented by the company. The added benefit derived by the company was exclusively based on outcomes on the change of the LDL-C value during a period of 24 weeks.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Research question C: patients in whom drug and dietary options to reduce lipid levels have been exhausted

2.5.1 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: 6 October 2015)
- bibliographical literature search on alirocumab (last search on 14 October 2015)
- search in trial registries for studies on alirocumab (last search on 6 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on alirocumab (last search on 18 November 2015)

No relevant study was identified from the check.

Study pool of the company

From the steps of information retrieval mentioned, the company identified one study relevant from the company's point of view. The ESCAPE study [21] was a double-blind RCT, in which adult patients with heterozygous familial hypercholesterolaemia were included who had regular LDL apheresis (every 1 or 2 weeks). Alirocumab + apheresis was compared with placebo + apheresis in the study. According to the company, the study was not yet completed at the time point of the submission of the dossier and there were no intermediate results yet. The company included the ESCAPE study as relevant in the benefit assessment, but presented no results for any of the outcomes. The study could therefore not be used for the present benefit assessment.

Furthermore, the treatment duration in the ESCAPE study was limited to 18 weeks; together with a follow-up phase of another 8 weeks, this resulted in a total study duration of notably less than one year. The study would therefore not be relevant for the benefit assessment even if results were available.

Hence no relevant data for the assessment of the added benefit of alirocumab in comparison with the ACT were available for research question C.

2.5.2 Results on added benefit

In its dossier, the company presented no relevant data for the assessment of the added benefit of alirocumab for research question C. This resulted in no hint of an added benefit of alirocumab in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit

The company presented no data for the assessment of the added benefit of alirocumab in patients unable to reach LDL-C goals and in whom drug and dietary options to reduce lipid levels have been exhausted. Hence an added benefit of alirocumab is not proven for these patients.

This deviates from the company's approach, which claimed that it could not assess the extent of added benefit at this time point, but expected an added benefit of alirocumab in comparison with LDL apheresis when the results of the ESCAPE study are available.

2.5.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.6 Extent and probability of added benefit – summary

Table 6 presents a summary of the extent and probability of the added benefit of alirocumab.

Table 6: Alirocumab – extent and probability of added benefit

Research question		**ACT**	**Extent and probability of added benefit**
A	Patients for whom statins are a treatment option[a, b]	Maximum tolerated drug and dietary treatment to reduce lipid levels	Added benefit not proven
B	Patients for whom statin treatment is not an option due to contraindications or treatment-limiting adverse events[b]	Other lipid-lowering drugs (**fibrates or anion exchangers or cholesterol resorption inhibitors**) as monotherapy	Added benefit not proven
C	Patients in whom drug and dietary lipid-lowering options have been exhausted	LDL apheresis (as "last resort" in refractory disease)[c]	Added benefit not proven

a: In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin.
b: According to the stipulations specified in the limitations of prescription for lipid-lowering drugs requiring prescription in Appendix III of the Pharmaceutical Directive [3].
c: Documented maximum tolerated drug and dietary treatment to reduce lipid for at least 12 months is the general prerequisite for LDL apheresis. Concomitant lipid-lowering drug and dietary treatment is possible and should be appropriately recorded.
ACT: appropriate comparator therapy; LDL: low-density lipoprotein; LDL-C: LDL cholesterol

An added benefit of alirocumab is not proven for any of the 3 research questions because no relevant studies were available in each case. This assessment deviates from that of the company. The company saw proof of a considerable added benefit for research question A, and an indication of a considerable added benefit for research question B; it made no statement on the added benefit for research question C.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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