IQWiG Reports – Commission No. A18-74

Alirocumab (primary hypercholesterolaemia and mixed dyslipidaemia) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of the executive summary of the dossier assessment *Alirocumab (primäre Hypercholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 January 2019). 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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. For the drug to be assessed, the pharmaceutical company (hereinafter referred to as the "company") submitted a dossier for early benefit assessment for the first time as per 2 November 2015. The company now requested a new benefit assessment in light of new scientific findings for some of the approved therapeutic indications. The assessment is based on a dossier compiled by the company. The dossier was submitted to IQWiG on 31 October 2018.

Research question

The aim of this report is to assess the added benefit of alirocumab in addition to diet-based therapy and, if appropriate, other lipid-lowering drugs compared with the appropriate comparator therapy (ACT) in patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

In its definition of the ACT, the G-BA differentiated among various patient groups. In terms of the assessment, this results in 2 research questions, which are presented in Table 2.

Table 2[2]: Research questions of the benefit assessment for alirocumab

Research question	Indication	ACT[a]
1	Patients eligible for statin therapy[b, c]	Maximally tolerated drug- and diet-based lipid-lowering therapy
2	Patients who are ineligible for statin therapy due to statin intolerance or contraindications[c]	Other (non-statin) lipid-lowering agents (fibrates, anion exchangers, cholesterol absorption inhibitors) as monotherapy and diet-based lipid-lowering therapy

a: Presentation of the respective ACT specified by the G-BA.
b: In combination with a statin or with a statin and other lipid-lowering therapeutic principles in patients who fail to achieve LDL-C levels with maximally tolerated statin therapy.
c: According to the prescribing restrictions for lipid-lowering prescription drugs specified in Annex III of the Drug Guideline.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL-C: low-density lipoprotein cholesterol

Patients who have exhausted drug- and diet-based options to lower lipid levels are not part of this assessment.

The assessment was 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

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

duration of 1 year were used for deriving any added benefit. This corresponds to the company's inclusion criteria.

Research question 1: Patients eligible for statin therapy

Study pool and study characteristics

The COMBO II study was included in the benefit assessment. The company already presented this study in its dossier during the first benefit assessment procedure for alirocumab. However, said study was unusable for the benefit assessment since the analyses submitted by the company included a considerable number of patients who had not been pretreated with maximally tolerated statin therapy. As part of the commenting procedure, the company submitted data on a relevant subpopulation of the study. The company's current dossier presents the final analyses of a relevant subpopulation of the study.

COMBO II is a double-blind, 2-arm RCT comparing alirocumab and ezetimibe, each in combination with statin-based lipid-lowering therapy. The study included patients with high cardiovascular risk whose low-density lipoprotein cholesterol (LDL-C) levels were not adequately controlled with existing statin therapy (≥ 70 mg/dL).

The primary outcome of the study was the change from baseline in LDL-C concentration at 24 weeks. Patient-relevant outcomes were mainly surveyed based on analyses of adverse events (AEs).

Alirocumab is approved only for patients who fail to reach LDL-C targets with maximally tolerated statin therapy. To meet the requirements under the marketing authorization, the company's dossier defined a subpopulation which had been pretreated with maximum statin therapy at the beginning of the study (mST population). This subpopulation comprised 262 patients in the alirocumab arm and 140 in the ezetimibe arm of the study.

This benefit assessment is based on the mST population and, unless stated otherwise, all data presented below refer to said population.

The benefit assessment is based on the final data analysis after 104 weeks of treatment.

Fibrates, bile acid sequestrants, cholesterol absorption inhibitors, nicotinic acid, and omega-3 fatty acids were used as further lipid-modifying agents, albeit only in a small percentage (between 10% and 15% at most) of patients.

Risk of bias

The risk of bias in the COMBO II study is low at both the study and the outcome levels. Therefore, at most hints, for instance of an added benefit, can be inferred from the available data.

Results

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found for the outcome of all-cause mortality. Consequently, there is no hint of added benefit of alirocumab + lipid-lowering therapy compared with ezetimibe + lipid-lowering therapy. An added benefit of alirocumab is therefore not proven for this outcome.

Morbidity

Combined cardiovascular outcome (MACE) and its individual components

Since the company presented no results for the relevant subpopulation, there are no usable data for the combined cardiovascular outcome of MACE.

No statistically significant difference was found between the study arms (with only a few events occurring in either treatment group) for any of the individual components: non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, and hospitalization for unstable angina pectoris. Overall, there is consequently no hint of added benefit of alirocumab + lipid-lowering therapy compared with ezetimibe + lipid-lowering therapy. An added benefit of alirocumab is therefore not proven.

Hospitalization for heart failure

No statistically significant difference between treatment groups was found for the outcome of hospitalization for heart failure. Consequently, there is no hint of added benefit of alirocumab + lipid-lowering therapy compared with ezetimibe + lipid-lowering therapy. An added benefit of alirocumab is therefore not proven for this outcome.

Health-related quality of life

The outcome of health-related quality of life was not surveyed in the COMBO II study. Consequently, there is no hint of added benefit of alirocumab + lipid-lowering therapy compared with ezetimibe + lipid-lowering therapy. An added benefit of alirocumab is therefore not proven for this outcome.

Adverse events

Sum total rates for SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of serious adverse events (SAEs) and discontinuation due to adverse events (AEs). Consequently, there is no hint of greater or lesser harm from alirocumab + lipid-lowering therapy compared with ezetimibe + lipid-lowering therapy. Greater or lesser harm from alirocumab is therefore not proven for these outcomes.

Specific AEs

No statistically significant differences between the treatment groups were found for any of the outcomes of allergic reactions and local reactions at the injection site. Consequently, there is no hint of greater or lesser harm from alirocumab + lipid-lowering therapy compared with ezetimibe + lipid-lowering therapy. Greater or lesser harm from alirocumab is therefore not proven for these outcomes.

OUTCOMES study additionally presented by the company

The OUTCOMES study included patients with acute coronary syndrome (ACS) who, despite subsequent treatment with statins and/or other lipid-lowering therapies, failed to reach the specified lipid levels.

The study is not suitable for deriving any conclusions on the added benefit of alirocumab in patients with primary hypercholesterolaemia or mixed dyslipidaemia who are eligible for statin therapy.

The patients included in the study failed to reach the desired LDL-C targets despite intensified therapy over several weeks, especially with statins. This means that all patients included in the study were in need of an escalation in terms of lipid-lowering therapy at the beginning of the study.

Following randomization, patients received either alirocumab or placebo in addition to the existing lipid-lowering background therapy. The background therapy was to be kept stable throughout the study. The existing therapy was thus escalated only in the patients in the alirocumab arm. In the placebo arm, only the existing treatment was continued even though the patients were in need of an escalation in terms of the lipid-lowering therapy.

Therefore, the ACT was not implemented. According to the research question (patients who fail to reach the LDL-C targets with the maximally tolerable statin dose), the appropriate lipid-lowering therapy needs to be escalated in order to adequately implement the ACT. However, such a therapy escalation was not provided in the comparator arm of the OUTCOMES study.

The OUTCOMES study is therefore irrelevant for the benefit assessment.

Research question 2: Patients who are ineligible for statin therapy due to statin intolerance or contraindications

The company again submitted the OUTCOMES study for patients who are ineligible for statin therapy due to statin intolerance or contraindication. It presented the results of a subpopulation which included only patients with statin intolerance or contraindication. The OUTCOMES study is irrelevant for the benefit assessment as the ACT was not implemented (see above). Therefore, no relevant data are available for research question 2.

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

On the basis of the results presented, the probability and extent of added benefit of the drug alirocumab in comparison with the ACT is assessed as follows:

Research question 1: Patients eligible for statin therapy

The COMBO II study shows no effects in favour or to the disadvantage of alirocumab. Therefore, for patients with primary (heterozygous familial or non-familial) hypercholesterolaemia or mixed dyslipidaemia who are eligible for statin therapy, there is no proof of an added benefit of alirocumab versus maximally tolerated drug- and diet-based lipid-lowering therapy.

Research question 2: Patients who are ineligible for statin therapy due to statin intolerance or contraindications

No relevant data are available to assess any added benefit of alirocumab in patients who are ineligible for statin therapy due to statin intolerance or contraindications. An added benefit of alirocumab is therefore not proven.

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

Table 3: Alirocumab – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Patients eligible for statin therapy[b, c]	Maximally tolerated drug- and diet-based lipid-lowering therapy	Added benefit not proven
Patients who are ineligible for statin therapy due to statin intolerance or contraindications[c]	Other (non-statin) lipid-lowering agents (fibrates, anion exchangers, cholesterol absorption inhibitors) as monotherapy and diet-based lipid-lowering therapy	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: In combination with a statin or with a statin and other lipid-lowering therapeutic principles in patients who fail to achieve LDL-C levels with maximally tolerated statin therapy.
c: According to the requirements of the Prescribing Restrictions Regarding Lipid-Lowering Prescription Drugs in Annex III of the German Drug Prescribing Directive.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LDL-C Low-density lipoprotein cholesterol

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. 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. 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].

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-74-alirocumab-primary-hypercholesterolaemia-or-mixed-dyslipidaemia-benefit-assessment-according-to-35a-social-code-book-v-new-scientific-findings.10910.html.