IQWiG Reports – Commission No. A20-91

Bempedoic acid/ezetimibe (primary hypercholesterolemia and mixed dyslipidemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.4 of the dossier assessment *Bempedoinsäure/Ezetimib (primäre Hypercholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 January 2021). 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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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.

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

List of abbreviations

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

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 fixed drug combination bempedoic acid/ezetimibe. 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 30 October 2020.

Research question

The aim of the present report was to assess the added benefit of bempedoic acid/ezetimibe as an adjunct to diet and, if appropriate, possibly in combination with a statin compared with the appropriate comparator therapy (ACT) in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

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

Table 2: Research questions of the benefit assessment of bempedoic acid/ezetimibe

Research question	Therapeutic indication	ACT[a]
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid/ezetimibe in accordance with the approval as an adjunct to diet in combination with a statin in patients who do not reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe, or as monotherapy in patients who are either statin-intolerant or for whom a statin is contraindicated and who are unable to reach LDL-C goals with ezetimibe alone, or in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
d. It is a general prerequisite for LDL apheresis that LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months.

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

The company followed the G-BA's specification of the ACT.

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 duration of 12 months were used for the derivation of the added benefit.

Results

Research question 1: patients in whom drug and dietary options to reduce lipid levels have not been exhausted

With its information retrieval, the company identified no study relevant to the benefit assessment. Nonetheless, the company presented the approval study 1002FDC-053 including the results as supplementary information. With a treatment duration of 12 weeks, this study is too short for the benefit assessment in the present therapeutic indication.

In its dossier, the company thus presented no suitable data for the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have not been exhausted. This resulted in no hint of an added benefit of bempedoic acid/ezetimibe in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted

In its dossier, the company presented no data for the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary lipid-lowering options have been exhausted. This resulted in no hint of an added benefit of bempedoic acid/ezetimibe 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 3 shows a summary of probability and extent of the added benefit of bempedoic acid/ezetimibe.

[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: Bempedoic acid/ezetimibe – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers	Added benefit not proven
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid/ezetimibe in accordance with the approval as an adjunct to diet in combination with a statin in patients who do not reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe, or as monotherapy in patients who are either statin-intolerant or for whom a statin is contraindicated and who are unable to reach LDL-C goals with ezetimibe alone, or in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive must be observed.
d. It is a general prerequisite for LDL apheresis that LDL-C cannot be lowered sufficiently with documented maximum dietary and drug treatment for at least 12 months.

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

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of bempedoic acid/ezetimibe as an adjunct to diet and, if appropriate, in combination with a statin compared with the ACT in adult patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

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

Table 4: Research questions of the benefit assessment of bempedoic acid/ezetimibe

Research question	Therapeutic indication	ACT[a]
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid/ezetimibe in accordance with the approval as an adjunct to diet in combination with a statin in patients who do not reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe, or as monotherapy in patients who are either statin-intolerant or for whom a statin is contraindicated and who are unable to reach LDL-C goals with ezetimibe alone, or in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [3] must be observed.
d. It is a general precondition for LDL apheresis that LDL-C cannot be lowered sufficiently with maximum dietary and drug treatment documented for 12 months [4].

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

The company followed the G-BA's specification on the ACT.

The assessment was 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 12 months were used for the derivation of the added benefit. This deviates from inclusion criteria of the company, which defined a minimum study duration of 24 weeks.

2.3 Research question 1: patients in whom drug and dietary options to reduce lipid levels have not been exhausted

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 lists on bempedoic acid/ezetimibe (status: 5 August 2020)
- bibliographical literature search on bempedoic acid/ezetimibe (last search on 5 August 2020)

- search in trial registries/trial results databases for studies on bempedoic acid/ezetimibe (last search on 5 August 2020)
- search on the G-BA website for bempedoic acid/ezetimibe (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on bempedoic acid (last search on 6 November 2020)

Concurring with the company, the check identified no relevant study.

The company did not identify any study relevant to the benefit assessment in its information retrieval, but it presented the approval study 1002FDC-053 [5] including the results as supplementary information. The company described that - with its treatment duration of 12 weeks - the study was too short for the benefit assessment and that the inclusion criteria of the study did not fully reflect the therapeutic indication of bempedoic acid/ezetimibe in the German health care context. Nevertheless, the company considers the results of the study to make an important contribution to the presentation of the medical benefit of bempedoic acid/ezetimibe.

The study 1002FDC-053 is a 4-arm, double-blind RCT comparing bempedoic acid/ezetimibe with each of the individual substances bempedoic acid and ezetimibe, each in a dosage compliant with the approval [6,7], and with placebo over 12 weeks. A total of 382 patients were randomly assigned to the study arms in a 2:2:2:1 ratio. The study included adults with documented atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolaemia and/or multiple cardiovascular risk factors, whose low-density lipoprotein cholesterol (LDL-C) level was elevated despite treatment with maximum tolerated statin therapy (LDL-C level ≥ 100 mg/dL for documented atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolaemia or ≥ 130 mg/dL in the presence of multiple cardiovascular risk factors). The individual maximum tolerated statin therapy was specified by the investigator based on her/his medical judgment and the local treatment standard, taking into account available sources including patient-reported history of lipid-lowering therapy; it could include statin regimens other than daily dosing, including no dose or a very low dose. The maximum tolerated statin therapy had to be stable for at least 4 weeks before the start of the study and was continued as lipid-lowering background therapy over the course of the study. Adjustments regarding the used substances or the dosage of this background therapy were not allowed over the course of the study.

The company compared the results of the bempedoic acid/ezetimibe arm with those of the ezetimibe arm and the placebo arm. From the point of view of the company, the ACT (maximum tolerated drug therapy as specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers) is represented in the placebo arm. The company justified the presentation of the comparison versus ezetimibe with the fact that,

according to the approval, bempedoic acid/ezetimibe is indicated for patients who are unable to reach LDL-C goals with ezetimibe alone.

The company's assessment that the duration of study 1002FDC-053 with a treatment duration of 12 weeks is too short for the benefit assessment is appropriate. The company itself defined a minimum study duration of 24 weeks, making reference to the guideline of the European Medicines Agency (EMA) on clinical investigation of medicinal products in the treatment of lipid disorders [8]. However, this study duration cannot be explicitly derived from the EMA guideline. This guideline rather considers a minimum study duration of 3 months to be sufficient for the investigation of drugs with known mechanisms of action. However, for other mechanism of action, a study duration of up to 12 months is recommended depending on the objective [8]. Moreover, the reasoning of the company is inconsistent, as in its dossier on the parallel benefit assessment of the individual substance bempedoic acid [9] it described that even a study duration of 24 weeks was insufficient to provide an adequate representation of the long-term treatment in the present therapeutic indication. Bempedoic acid/ezetimibe is used as long-term treatment of chronic diseases with the primary goal of lowering the LDL-C value to reduce the cardiovascular risks. Therefore, a study duration of at least 12 months is considered reasonable for the assessment of long-term effects of bempedoic acid/ezetimibe on patient-relevant outcomes, particularly on cardiovascular events, in the present therapeutic indication. This is consistent with the approach taken in previous dossier assessments on substances also used for lipid lowering (alirocumab [10,11], evolocumab [12,13], lomitapide [14]).

In addition to the fact that study 1002FDC-053 was too short, the G-BA's ACT was not implemented for research question 1 in the placebo arm since patients received no further active therapy in addition to their inadequate lipid-lowering background therapy despite elevated LDL-C levels (see above). According to the stipulations of the G-BA in its specification of the ACT, continuation of an inadequate therapy in the course of the study does not correspond to the implementation of the ACT if the maximum tolerated drug treatment has not yet been exhausted.

Irrespective of this, the included patients do not correspond to the therapeutic indication of bempedoic acid/ezetimibe [15], because only about 1.4% of the patients had been pretreated with ezetimibe. This is cited by the company as a limitation of transferability to the German health care context.

Approach of the company for the derivation of an added benefit

Although the company itself described that no relevant studies were available for the benefit assessment, it ultimately derived a hint of a non-quantifiable added benefit for research question 1. This was not appropriate. The assessment of the added benefit of bempedoic acid/ezetimibe would require comparative data on the adequately implemented ACT for the patient population relevant for the approval over a period of at least 12 months. The company did not present such data.

2.3.2 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have not been exhausted. This resulted in no hint of an added benefit of bempedoic acid/ezetimibe in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

An added benefit is not proven since the company presented no data for the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary lipid-lowering options have not been exhausted.

This deviates from the company's assessment, which derived a hint of non-quantifiable added benefit.

2.4 Research question 2: patients in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted

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 lists on bempedoic acid/ezetimibe (status: 5 August 2020)
- bibliographical literature search on bempedoic acid/ezetimibe (last search on 5 August 2020)
- search in trial registries/trial results databases for studies on bempedoic acid/ezetimibe (last search on 5 August 2020)
- search on the G-BA website for bempedoic acid/ezetimibe (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on bempedoic acid (last search on 6 November 2020)

Concurring with the company, the check identified no relevant study.

2.4.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in

whom drug and dietary lipid-lowering options have been exhausted. This resulted in no hint of an added benefit of bempedoic acid/ezetimibe in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

An added benefit is not proven since the company presented no data for the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary lipid-lowering options have been exhausted.

This concurs with the company's assessment.

2.4.4 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of bempedoic acid/ezetimibe in comparison with the ACT is summarized in Table 5.

Table 5: Bempedoic acid/ezetimibe – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug and dietary options to reduce lipid levels have not been exhausted[b, c]	Maximum tolerated drug treatment specified by the physician under consideration of statins, cholesterol absorption inhibitors and anion exchangers	Added benefit not proven
2	Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in whom drug (except evolocumab) and dietary options to reduce lipid levels have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as "last resort" in refractory disease)[d] possibly with concomitant lipid-lowering drug treatment	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Use of bempedoic acid/ezetimibe in accordance with the approval as an adjunct to diet in combination with a statin in patients who do not reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe, or as monotherapy in patients who are either statin-intolerant or for whom a statin is contraindicated and who are unable to reach LDL-C goals with ezetimibe alone, or in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.
c. The stipulations regarding the limitations of prescription of Appendix III of the Pharmaceutical Directive [3] must be observed.
d. It is a general precondition for LDL apheresis that LDL-C cannot be lowered sufficiently with maximum dietary and drug treatment documented for 12 months [4].

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

The G-BA decides on the added benefit.

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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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