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Inclisiran (primary hypercholesterolaemia or mixed dyslipidaemia) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Inclisiran (primäre Hypercholesterinämie und gemischte Dyslipidämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2021). 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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[2] 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)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

The Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) in accordance with § 35a Social Code Book (SGB) V to assess the benefit of the drug inclisiran. 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 1 February 2021.

Research question

The aim of this report is to assess the added benefit of inclisiran as an adjunct to dietary therapy and, if necessary, statin and/or other lipid-lowering therapies in comparison with the appropriate comparative therapy (ACT) in adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia.

The G-BA's specification of the ACT results in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of inclisiran

Research question	Indication	ACT[a]
1	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmacological options for lipid lowering have not been exhausted[b, c]	Maximum tolerated drug dose upon the physician's discretion, taking into account statins, cholesterol absorption inhibitors, and anion exchange resins
2	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom all dietary and pharmaceutical options for lipid lowering (except evolocumab) have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as an option of last resort in therapy-resistant cases)[d], if necessary with concomitant lipid-lowering medication.

a. Presented is the ACT specified by the G-BA.
b. Use of inclisiran as per approval in addition to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who fail to reach LDL-C targets on the maximum tolerable statin dose or as monotherapy or in combination with other lipid-lowering therapies in patients with statin intolerance or statin contraindication.
c. The specifications regarding prescription restrictions as per Pharmaceutical Guideline (AM-RL) Appendix III must be observed.
d. Generally, the prerequisite for LDL apheresis therapy is 12 months of documented maximum dietary and pharmacological treatment without sufficient reduction of LDL-C.

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 12 months were used to derive added benefit. This deviates from the company's inclusion criteria, which specified a shorter minimum duration of 24 weeks.

Results

The company did not present any data for assessing the added benefit of inclisiran in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmacological options for lipid lowering have not been exhausted (research question 1) or have been exhausted except for evolocumab (research question 2). For both research questions, this results in no hint of any added benefit of inclisiran 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 presents a summary of the probability and extent of added benefit of inclisiran.

Table 3: Inclisiran – probability and extent of added benefit

Research question	Indication	ACT[a]	Probability and extent of added benefit
1	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmacological options for lipid lowering have not been exhausted[b, c]	Maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins, cholesterol absorption inhibitors, and anion exchange resins	Added benefit not proven
2	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom all dietary and pharmacological options for lipid lowering (except evolocumab) have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as an "ultima ratio" in therapy-resistant cases)[d], if necessary with concomitant lipid-lowering medication.	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Use of inclisiran as per approval in addition to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who fail to reach LDL-C targets on the maximum tolerable statin dose or as monotherapy or in combination with other lipid-lowering therapies in patients with statin intolerance or statin contraindication.
c. The specifications regarding prescription restrictions as per Pharmaceutical Guideline (AM-RL) Appendix III must be observed.
d. Generally, the prerequisite for LDL apheresis therapy is 12 months of documented maximum dietary and pharmacological treatment without sufficient reduction of LDL-C.

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.

[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].

2.2 Research question

The aim of this report is to assess the added benefit of inclisiran as an adjunct to dietary therapy and, if necessary, statin and/or other lipid-lowering therapies in comparison with the ACT in adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia.

The G-BA's specification of the ACT results in the research questions presented in Table 4.

Table 4: Research questions of the benefit assessment of inclisiran

Research question	Indication	ACT[a]
1	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmacological options for lipid lowering have not been exhausted[b, c]	Maximum tolerated drug dose upon the physician's discretion, taking into account statins, cholesterol absorption inhibitors, and anion exchange resins
2	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom all dietary and pharmacological options for lipid lowering (except evolocumab) have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as an "ultima ratio" in therapy-resistant cases)[d], if necessary with concomitant lipid-lowering medication.

a. Presented is the ACT specified by the G-BA.
b. Use of inclisiran as per approval in addition to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who fail to reach LDL-C targets on the maximum tolerable statin dose or as monotherapy or in combination with other lipid-lowering therapies in patients with statin intolerance or statin contraindication.
c. The specifications regarding prescription restrictions as per Pharmaceutical Guideline (AM-RL) Appendix III [3] must be observed.
d. Generally, the prerequisite for LDL apheresis therapy is 12 months of documented maximum dietary and pharmacological treatment without sufficient reduction of LDL-C [4].

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

The company departs from the ACT specified by the G-BA in that the company identified an additional 3rd group of patients within the therapeutic indication, namely those ineligible for statin therapy due to contraindications or treatment-limiting side effects. The ACT designated by the company for its additional patient group consisted of lipid-lowering drugs other than statins (anion exchange resins, cholesterol absorption inhibitors) in the form of lipid-lowering monotherapy. The company failed to soundly justify the need for its addition of a 3rd research question.

The deviation from the G-BA's specification in the form of an additionally identified research question is not persuasive. Patients with statin intolerance or contraindication are covered by research questions 1 and 2, which result from the ACT specified by the G-BA.

Since the company failed to identify any relevant study for its research questions, the company's approach is of no consequence for the benefit assessment. In this report, the check for studies excluded from the dossier is described for both research questions jointly.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 12 months were used to derive added benefit. This deviates from the company's inclusion criteria, which specified a shorter minimum duration of 24 weeks.

2.3 Research question 1: Patients in whom dietary and pharmacological options for lipid lowering 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 cited by the company in the dossier:

- Study list on inclisiran (as of 2 December 2020)
- Bibliographic literature search on inclisiran (most recent search on 1 December 2020)
- Search in trial registries / study results databases on inclisiran (most recent search on 2 December 2020)
- Search on the G-BA website on inclisiran (most recent search on 2 December 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on inclisiran (most recent search on 17 February 2021)

Consistent with the company's results, no relevant study was identified.

Out of the 6 studies it cited on its study list, including the 3 approval studies of inclisiran, the company excluded 5 studies due to a "different comparator therapy". None of these studies allowed modifying the lipid-lowering therapy administered at baseline in the course of the study [5-11]. Hence, it is appropriate for the company to exclude these studies. For the ongoing study ORION-4, only limited information is currently available [12]. It is unclear to what extent the study meets the inclusion criteria of the benefit assessment. Results are expected no earlier than December 2024 [13].

2.3.2 Results on added benefit

The company has presented no data for adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmaceutical options for lipid lowering have not been exhausted. Hence, there is no hint of

added benefit of inclisiran in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

The company has presented no data for assessing any added benefit of inclisiran in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmaceutical options for lipid lowering have not been exhausted. An added benefit is therefore not proven.

This rating concurs with the company's assessment.

2.4 Research question 2: Patients in whom dietary and pharmaceutical options for lipid lowering (except evolocumab) 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 cited by the company in the dossier:

- Study list on inclisiran (as of 2 December 2020)
- Bibliographic literature search on inclisiran (most recent search on 1 December 2020)
- Search in trial registries / study results databases on inclisiran (most recent search on 2 December 2020)
- Search on the G-BA website on inclisiran (most recent search on 2 December 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on inclisiran (most recent search on 17 February 2021)

Consistent with the company's results, no relevant study was identified (see Section 2.3.1 for a discussion).

2.4.2 Results on added benefit

The company has presented no data for adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmaceutical options for lipid lowering (except evolocumab) have been exhausted. Hence, there is no hint of added benefit of inclisiran in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company has presented no data for assessing any added benefit of inclisiran in comparison with the ACT for adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmaceutical options for lipid lowering (except evolocumab) have been exhausted. An added benefit is therefore not proven.

This rating concurs with the company's assessment.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results regarding the benefit assessment of inclisiran in comparison with the ACT.

Table 5: Inclisiran – probability and extent of added benefit

Research question	Indication	ACT[a]	Probability and extent of added benefit
1	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom dietary and pharmacological options for lipid lowering have not been exhausted[b, c]	Maximum tolerated pharmacological therapy upon the physician's discretion, taking into account statins, cholesterol absorption inhibitors, and anion exchange resins	Added benefit not proven
2	Adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia in whom all dietary and pharmacological options for lipid lowering (except evolocumab) have been exhausted[b, c]	Evolocumab[c] or LDL apheresis (as an "ultima ratio" in therapy-resistant cases)[d], if necessary with concomitant lipid-lowering medication.	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Use of inclisiran as per approval in addition to diet in combination with a statin or a statin together with other lipid-lowering therapies in patients who fail to reach LDL-C targets on the maximum tolerable statin dose or as monotherapy or in combination with other lipid-lowering therapies in patients with statin intolerance or statin contraindication.
c. The specifications regarding prescription restrictions as per Pharmaceutical Guideline (AM-RL) Appendix III [3] must be observed.
d. Generally, the prerequisite for LDL apheresis therapy is 12 months of documented maximum dietary and pharmacological treatment without sufficient reduction of LDL-C [4].

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

The above assessment concurs with that of the company.

The G-BA decides on the added benefit.

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/a21-13.html.