Linzagolix
(uterine fibroid symptoms)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Linzagolix (Uterusmyome) – Nutzenbewertung gemäß § 35a SGB V*. 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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No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug linzagolix. 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 10 September 2024.

Research question

The aim of this report is to assess the added benefit of linzagolix compared to the appropriate comparator therapy (ACT) in adult women of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of linzagolix

Therapeutic indication	**ACT[a]**
Adult women of reproductive age with moderate to severe symptoms of uterine fibroids	Individualized treatment[b, c] depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ symptom-oriented treatment: ▫ relugolix/estradiol/norethisterone acetate ▫ progestogens taking into account the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed) ▪ invasive treatment options
a. Presented is the ACT specified by the G-BA. b. The G-BA points out that there is a relevant proportion of patients who decide against drug or surgical intervention. In the present case, it is a pharmacological intervention, so these patients are not eligible for the present intervention. Against the background of the drug character of the intervention, an active therapy is determined as ACT irrespective of the patient's decision. c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made at the start of the study before group allocation (e.g. randomization). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Results

The check of completeness of the study pool did not identify any relevant study for assessing the added benefit of linzagolix in comparison with the G-BA's ACT.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of linzagolix 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 linzagolix.

[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: Linzagolix – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult women of reproductive age with moderate to severe symptoms of uterine fibroids	Individualized treatment[b, c] depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ symptom-oriented treatment: ▫ relugolix/estradiol/norethisterone acetate ▫ progestogens taking into account the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed) ▪ invasive treatment options	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The G-BA points out that there is a relevant proportion of patients who decide against drug or surgical intervention. In the present case, it is a pharmacological intervention, so these patients are not eligible for the present intervention. Against the background of the drug character of the intervention, an active therapy is determined as ACT irrespective of the patient's decision.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made at the start of the study before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of linzagolix compared to the ACT in adult women of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of linzagolix

Therapeutic indication	**ACT[a]**
Adult women of reproductive age with moderate to severe symptoms of uterine fibroids	Individualized treatment[b, c] depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ symptom-oriented treatment: ▫ relugolix/estradiol/norethisterone acetate ▫ progestogens taking into account the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed) ▪ invasive treatment options

a. Presented is the ACT specified by the G-BA.
b. The G-BA points out that there is a relevant proportion of patients who decide against drug or surgical intervention. In the present case, it is a pharmacological intervention, so these patients are not eligible for the present intervention. Against the background of the drug character of the intervention, an active therapy is determined as ACT irrespective of the patient's decision.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made at the start of the study before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on linzagolix (status: 22 July 2024)
- bibliographical literature search on linzagolix (last search on 05 July 2024)
- search in trial registries/trial results databases for studies on linzagolix (last search on 19 July 2024)
- search on the G-BA website for linzagolix (last search on 31 July 2024)
- bibliographical literature search on the ACT (last search on 05 July 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 19 July 2024)
- search on the G-BA website for the ACT (last search on 31 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on linzagolix (last search on 20 September 2024); for search strategies, see I Appendix A of the full dossier assessment

In agreement with the company, the check of completeness of the study pool did not identify any relevant study for assessing the added benefit of linzagolix in comparison with the G-BA's ACT.

The company supportively presented the approval studies PRIMROSE 1 [3,4] and PRIMROSE 2 [3,5], each of which compares linzagolix with placebo, for the description of the medical benefit. In both studies, the use of all treatment options listed in the G-BA's ACT (see Table 4) was prohibited during the entire study phase. Consequently, an active therapy in the sense of the ACT was not implemented for patients under treatment with placebo in PRIMROSE 1 and PRIMROSE 2. Concurring with the company, the studies PRIMROSE 1 and PRIMROSE 2 are assessed as unsuitable for the assessment of the added benefit of linzagolix due to the lack of comparison with the ACT.

As the company did not identify a suitable study for the direct comparison, it conducted a search for studies that might be considered for indirect comparisons of linzagolix versus the ACT via the common comparator placebo. In its information retrieval, the company identified several studies that compared individual drugs listed in the ACT with placebo. The company considered these studies to be unsuitable for conducting an indirect comparison with the studies PRIMROSE 1 and/or PRIMROSE 2 in the present research question and therefore did not present an indirect comparison. Thus, for the present assessment, neither results from studies of direct comparison nor from indirect comparisons are available.

I 4 Results on added benefit

The company's dossier provides no suitable data for the assessment of linzagolix for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age versus the ACT. There is no hint of an added benefit of linzagolix in comparison with the ACT. An added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Linzagolix – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult women of reproductive age with moderate to severe symptoms of uterine fibroids	Individualized treatment[b, c] depending on the type and the severity of the symptoms as well as the patient's symptom burden, selecting from: ▪ symptom-oriented treatment: ▫ relugolix/estradiol/norethisterone acetate ▫ progestogens taking into account the respective approval status (for patients for whom symptomatic treatment of prolonged and/or heavy periods [menorrhagia, hypermenorrhoea] is sufficient) ▫ ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolization and/or surgery are not suitable or have failed) ▪ invasive treatment options	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The G-BA points out that there is a relevant proportion of patients who decide against drug or surgical intervention. In the present case, it is a pharmacological intervention, so these patients are not eligible for the present intervention. Against the background of the drug character of the intervention, an active therapy is determined as ACT irrespective of the patient's decision.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made at the start of the study before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-92.html.