Linzagolix (endometriosis)

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 (Endometriose) – 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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Linzagolix, Endometriosis, Benefit Assessment

Medical and scientific advice

No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

No patients or families were involved in 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) 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 16 December 2024.

Research question

The aim of this report is to assess the added benefit of linzagolix in comparison with the appropriate comparator therapy (ACT) for symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis.

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

Table 2: Research question of the benefit assessment of linzagolix

Therapeutic indication	**ACT**[a]
Symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis; with concomitant hormonal add-back therapy[b]	Individualized treatment[c, d] taking into account previous treatment, possible organ destruction and location and extent of the endometriotic lesions, selecting from ▪ dienogest ▪ GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin) ▪ relugolix/estradiol/norethisterone acetate ▪ surgical procedures
a. Presented is the ACT specified by the G-BA. b. According to the SPC for linzagolix, the hormonal add-back therapy consists of estradiol and norethisterone acetate. c. Adequate pain therapy should be offered in the study arms. d. For the implementation of individualized therapy in a study of direct comparison, the investigators are 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). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). A rationale must be provided for the choice and any limitation of treatment options. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; SPC: Summary of Product Characteristics	

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.

Table 3: Linzagolix – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis; with concomitant hormonal add-back therapy[b]	Individualized treatment[c, d] taking into account previous treatment, possible organ destruction and location and extent of the endometriotic lesions, selecting from ▪ dienogest ▪ GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin) ▪ relugolix/estradiol/norethisterone acetate ▪ surgical procedures	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the SPC for linzagolix, the hormonal add-back therapy consists of estradiol and norethisterone acetate.
c. Adequate pain therapy should be offered in the study arms.
d. For the implementation of individualized therapy in a study of direct comparison, the investigators are 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). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; SPC: Summary of Product Characteristics

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].

I 2 Research question

The aim of this report is to assess the added benefit of linzagolix in comparison with the ACT for symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis.

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

Table 4: Research question of the benefit assessment of linzagolix

Therapeutic indication	**ACT**[a]
Symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis; with concomitant hormonal add-back therapy[b]	Individualized treatment[c, d] taking into account previous treatment, possible organ destruction and location and extent of the endometriotic lesions, selecting from ▪ dienogest ▪ GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin) ▪ relugolix/estradiol/norethisterone acetate ▪ surgical procedures
a. Presented is the ACT specified by the G-BA. b. According to the SPC for linzagolix [3], the hormonal add-back therapy consists of estradiol and norethisterone acetate. c. Adequate pain therapy should be offered in the study arms. d. For the implementation of individualized therapy in a study of direct comparison, the investigators are 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). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). A rationale must be provided for the choice and any limitation of treatment options. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; SPC: Summary of Product Characteristics	

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 lists on linzagolix (status: 18 November 2024)
- bibliographical literature search on linzagolix (last search on 30 October 2024)
- search in trial registries/trial results databases for studies on linzagolix (last search on 6 November 2024)
- search on the G-BA website for linzagolix (not conducted)
- bibliographical literature search on the ACT (last search on 30 October 2024)
- search in trial registries/trial results databases for studies on the ACT (last search on 6 November 2024)
- search on the G-BA website for the ACT (not conducted)

To check the completeness of the study pool:

- search in trial registries for studies on linzagolix (last search on 2 January 2025); 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 provided a supportive presentation of the pivotal studies EDELWEISS 2 [4], EDELWEISS 3 [5,6] and EDELWEISS 6 (extension study pf EDELWEISS 3) [7] to describe the medical benefit.

In EDELWEISS 2 and EDELWEISS 3, linzagolix (200 mg in combination with an add-back therapy, and 75 mg) was compared with placebo. In both studies, none of the treatment options listed in the G-BA's ACT (see Table 4) was not allowed during the entire study phase. Consequently, active therapy in the sense of the ACT was not implemented for patients under treatment with placebo in EDELWEISS 2 and EDELWEISS 3. The EDELWEISS 6 extension study compared linzagolix at a dose of 200 mg in combination with add-back therapy with linzagolix at a dose of 75 mg. Hence there was no comparison with the ACT.

Concurring with the company, EDELWEISS 2, EDELWEISS 3 and EDELWEISS 6 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 potentially relevant common comparators placebo and linzagolix at a dose of 75 mg. In its information retrieval, the company identified several studies that compared individual drugs listed in the ACT with placebo or linzagolix at a dose of 75 mg. The company considered these studies to be unsuitable for conducting an indirect comparison with EDELWEISS 2, EDELWEISS 3 and/or EDELWEISS 6 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 contains no data for the assessment of linzagolix for symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis. 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**
Symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis; with concomitant hormonal add-back therapy[b]	Individualized treatment[c, d] taking into account previous treatment, possible organ destruction and location and extent of the endometriotic lesions, selecting from ▪ dienogest ▪ GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin) ▪ relugolix/estradiol/norethisterone acetate ▪ surgical procedures	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the SPC for linzagolix [3], the hormonal add-back therapy consists of estradiol and norethisterone acetate.
c. Adequate pain therapy should be offered in the study arms.
d. For the implementation of individualized therapy in a study of direct comparison, the investigators are 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). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; SPC: Summary of Product Characteristics

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.

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/a24-123.html.