Relugolix/estradiol/norethisterone acetate (endometriosis)

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

EXTRACT

Project: A23-117 Version: 1.0 Status: 27 Feb 2024 DOI: 10.60584/A23-117_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Relugolix/Estradiol/Norethisteronacetat (Endometriose) – Nutzenbewertung gemäß § 35a SGB V*. 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Relugolix/estradiol/norethisterone acetate (endometriosis) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

29 November 2023

Internal Project No.

A23-117

DOI-URL

https://doi.org/10.60584/A23-117_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the Endometriosis Association Germany (Endometriose-Vereinigung Deutschland e. V.) for participating in the written exchange and for its support. The Endometriosis Association Germany was not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Caroline Wöhl
- Christiane Balg
- Erika Baumbach
- Lars Beckmann
- Tatjana Hermanns
- Prateek Mishra
- Kristina Schaubert
- Volker Vervölgyi

Keywords

Relugolix, Estradiol, Norethindrone Acetate, Endometriosis, Benefit Assessment

Part I: Benefit assessment

I Table of contents

Page

I List of tables[2]

Page

[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
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
E2	estradiol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NETA	norethisterone acetate
RCT	randomized controlled trial
SAE	serious adverse event
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 combination relugolix/estradiol/norethisterone acetate. 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 29 November 2023.

Research question

The aim of the present report is the assessment of the added benefit of the fixed combination relugolix, estradiol (E2) and norethisterone acetate (NETA) (hereinafter referred to as "relugolix/E2/NETA") in comparison with the appropriate comparator therapy (ACT) for the symptomatic treatment of endometriosis in adult women of reproductive age who have already been treated with medication or surgery.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of relugolix/E2/NETA

Research question	Therapeutic indication	ACT[a]
1	Symptomatic treatment of endometriosis in adult women of reproductive age who have already been treated with medication or surgery and who are candidates for treatment with dienogest [b]	Dienogest[c]
2	Symptomatic treatment of adult women of reproductive age with endometriosis who have already been treated with medication or surgery and who are no (longer) candidates for treatment with dienogest[b]	GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin)[c]

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that for patients with endometriosis who are candidates for treatment with relugolix/E2/NETA, invasive treatment options are not considered at the current treatment time.
c. Adequate pain therapy should be offered in both study arms.

ACT: appropriate comparator therapy; E2: estradiol; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; NETA: norethisterone acetate

The company followed the G-BA's specifications neither regarding the categorization of the therapeutic indication into the 2 patient groups nor for the defined ACT. Instead, it specified an individualized treatment for the entire target population in the present therapeutic indication, taking into account the symptoms, localization and extent of the endometriosis lesions, prior therapies, and the patient's preferences, selecting analgesics (level 1 and level 2

according to the World Health Organisation [WHO] step-by-step scheme), gonadotropin-releasing hormone (GnRH) receptor agonists and invasive treatment options as comparator therapy. The company's justification for deviating from the patient population and ACT is not plausible. In line with the G-BA's specification, the present assessment is conducted separately for the 2 research questions, each in comparison with the ACT specified by the G-BA. Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

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 were used for deriving any added benefit.

Results

No relevant study comparing Relugolix/E2/NETA with the respective ACT specified by the G-BA in the present therapeutic indication was identified for either research question 1 or research question 2.

The company deviated from the G-BA's specification and instead cited an individualized treatment as the ACT. The company used the RCTs SPIRIT 1 and SPIRIT 2 for the assessment of added benefit in its jointly analysed patient group. However, no suitable data for the benefit assessment were presented with these 2 RCTs - neither compared to the comparator therapy selected by the company nor compared to the ACT specified by the G-BA. This is explained below.

Evidence presented by the company – studies SPIRIT-1 and SPIRIT-2

For the assessment of added benefit, the company presented a meta-analysis of the 2 RCTs SPIRIT 1 and SPIRIT 2 (relugolix + E2/NETA: N = 418 vs. placebo: N = 416). The studies SPIRIT 1 and SPIRIT 2 have identical study designs (so-called twin studies); both studies are double-blind RCTs comparing relugolix + E2/NETA (free combination) with placebo. Premenopausal women from 18 up to 50 years inclusively with moderate to severe endometriosis pain were included. Prior endometriosis therapy with medication or surgery was not an inclusion criterion.

In both studies, the use of level 1 and level 2 analgesics defined in the study protocol as rescue medication were permitted as concomitant treatment during the course of the study.

Both studies comprise a single-blind run-in phase of 35 to 70 days, a double-blind, randomized treatment phase of 24 weeks and a subsequent safety follow-up visit (approx. 30 days after the last dose of the study medication).

Co-primary outcomes of the SPIRIT 1 and SPIRIT 2 studies are the proportion of patients with a clinically relevant reduction in dysmenorrhoea at week 24 compared to baseline without an increase in analgesic consumption and the proportion of patients with a clinically relevant reduction in non-menstrual pelvic pain at week 24 compared to baseline without an increase in analgesic consumption.

Assessment of the evidence presented by the company

Failure of SPIRIT 1 and SPIRIT 2 studies to implement the G-BA's specifications regarding patient population and ACT

The company's dossier examined only 1 research question under which it jointly analysed all patients in the present therapeutic indication. The data presented by the company are not suitable for assessing the added benefit of relugolix/E2/NETA compared with the ACT in the 2 research questions of the G-BA.

Regardless, the G-BA's ACT was not implemented in the respective placebo arm of the two studies with the administered concomitant therapy in both research questions. In all study arms, patients received rescue medication as required to relieve endometriosis-associated pain with level 1 and level 2 analgesics permitted under the study protocol. However, the administration of both progestogens (research question 1) and GnRH analogues (research question 2) was prohibited. Thus, both studies cannot answer the research questions on the benefit assessment of relugolix/E2/NETA.

The comparator therapy specified by the company was not implemented in the SPIRIT 1 and SPIRIT 2 studies.

In deviation from the definition of the G-BA, the company named an individualized treatment with a choice of analgesics, GnRH receptor agonists and invasive treatment options as comparator therapy for the entire target population in the present therapeutic indication, but with the 2 RCTs SPIRIT 1 and SPIRIT 2 it did not present any suitable studies for an adequate comparison of relugolix/E2/NETA with the comparator therapy chosen by it; neither surgical treatment of endometriosis nor the use of GnRH analogues was permitted. The company's argument that a comparison with level 1 and level 2 analgesics in the context of a single-comparator study is justified for the implementation of individualized treatment was assessed as inappropriate. Since treatment with relugolix/E2/NETA corresponds to a therapy approach with medication or surgery, it is assumed that (renewed) hormonal therapy to induce therapeutic amenorrhoea is an option for patients in the present therapeutic indication. Therefore, the sole administration of analgesics for the treatment of pain is not an adequate therapy for this patient population.

With respect to both studies, 542 of 834 (65%) patients had not undergone prior hormonal therapy, meaning that in principle they would have been candidates for treatment with

dienogest. Of the 292 patients who had undergone prior hormonal therapy, 167 (57%) had already received treatment with dienogest, meaning that dienogest treatment was no longer a treatment option for them. As only a small proportion of patients in both studies had undergone prior therapy with GnRH analogues (SPIRIT 1: 14 % vs. 13 %; SPIRIT 2: 5 % vs. 5 %), it can be assumed that hormonal treatment with GnRH analogues would still have been an option for the majority of patients.

In summary, by presenting the SPIRIT 1 and SPIRIT 2 studies, the company presented neither suitable studies compared with the comparator therapy selected by it nor compared with the ACT specified by the G-BA in each case.

Results on added benefit

There are no suitable data available for assessing the added benefit of relugolix/estradiol/NETA compared to the ACT for the symptomatic treatment of endometriosis in women of reproductive age who have already been treated with medication or surgery. There is no hint of added benefit of relugolix/E2/NETA in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven for either of them.

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

Table 3 summarizes the probability and extent of added benefit of relugolix/E2/NETA.

[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: Relugolix/E2/NETA – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Symptomatic treatment of endometriosis in adult women of reproductive age who have already been treated with medication or surgery and who are candidates for treatment with dienogest [b]	Dienogest[c]	Added benefit not proven
2	Symptomatic treatment of adult women of reproductive age with endometriosis who have already been treated with medication or surgery and who are no (longer) candidates for treatment with dienogest[b]	GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin)[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that for patients with endometriosis who are candidates for treatment with relugolix/E2/NETA, invasive treatment options are not considered at the current treatment time.
c. Adequate pain therapy should be offered in both study arms.

ACT: appropriate comparator therapy; E2: estradiol; G-BA: Federal Joint Committee; NETA: GnRH: gonadotropin-releasing hormone; norethisterone acetate

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of the fixed combination relugolix, estradiol (E2) and norethisterone acetate (NETA) (hereinafter referred to as "relugolix/E2/NETA") in comparison with the appropriate comparator therapy (ACT) for the symptomatic treatment of endometriosis in adult women of reproductive age who have already been treated with medication or surgery.

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

Table 4: Research question of the benefit assessment of relugolix/E2/NETA

Research question	Therapeutic indication	ACT[a]
1	Symptomatic treatment of endometriosis in adult women of reproductive age who have already been treated with medication or surgery and who are candidates for treatment with dienogest [b]	Dienogest[c]
2	Symptomatic treatment of adult women of reproductive age with endometriosis who have already been treated with medication or surgery and who are no (longer) candidates for treatment with dienogest[b]	GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin)[c]

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that for patients with endometriosis who are candidates for treatment with relugolix/E2/NETA, invasive treatment options are not considered at the current treatment time.
c. Adequate pain therapy should be offered in both study arms.

ACT: appropriate comparator therapy; E2: estradiol; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; NETA: norethisterone acetate

In deviation from the G-BA's definition of the ACT, the company does not divide the patient population into patients for whom treatment with dienogest is an option and patients for whom treatment with dienogest is not (no longer) an option. The company's justification for the deviation from the categorisation of the patient population and from the ACT is not appropriate (see the following section and Chapter I 3). In line with the G-BA's specification, the present assessment is conducted separately for the 2 research questions, each in comparison with the ACT specified by the G-BA. Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

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 were used for deriving any added benefit. This concurs with the company's inclusion criteria.

Deviation from the specified patient population and ACT

The company followed the G-BA's specifications neither regarding the categorization of the therapeutic indication into the 2 patient groups nor for the defined ACT. Instead, it specified an individualized treatment for the entire target population in the present therapeutic indication, taking into account the symptoms, localization and extent of the endometriosis lesions, prior therapies, and the patient's preferences, selecting analgesics (level 1 and level 2 according to the World Health Organisation [WHO] step-by-step scheme), gonadotropin-releasing hormone (GnRH) receptor agonists and invasive treatment options as comparator therapy. From the company's point of view, a single-comparator study is suitable if it was conducted against 1 of the 3 mentioned treatment options.

As justification, the company states in Module 3 B of the full dossier that relugolix/E2/NETA is only indicated after failure of first-line therapy and that dienogest would therefore not be considered as an ACT in the present therapeutic indication. In the company's opinion, it can be assumed that all patients with endometriosis are initially treated with dienogest in accordance with the requirements of the S2k guideline on endometriosis [3] and are only eligible for treatment with relugolix/E2/NETA after treatment failure or insufficient response to treatment with dienogest. This justification by the company for deviating from the patient population and ACT is not appropriate. Relugolix/E2/NETA is approved for the symptomatic treatment of endometriosis in patients who have undergone prior endometriosis therapy with medication or surgery [4]. The marketing authorisation therefore also covers patients who have not previously been treated with hormonal therapy. Since a clear recommendation for progestogens (dienogest) as a first-line agent can be derived from the S2k guideline cited by the company and the written participation of scientific and medical societies to determine the ACT for patients without prior hormonal therapy for their endometriosis, dienogest is generally considered as a treatment option for patients with previous surgical or drug-based, non-hormonal treatment [3,5]. According to the S2k guideline, the GnRH analogues approved for the treatment of endometriosis can be used as part of hormonal therapy, as also described by the company in Module 3 B of the full dossier, after treatment failure on dienogest. The company, however, considers GnRH receptor agonists to be only a possible treatment option for an individualized treatment for the entire target population in the present therapeutic indication - regardless of suitability for treatment with dienogest.

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 relugolix/E2/NETA (status: 12 October 2023)
- bibliographical literature search on relugolix/E2/NETA (last search on 8 October 2023)
- search in trial registries/trial results databases for studies on relugolix/E2/NETA (last search on 8 October 2023)
- search on the G-BA website for relugolix/E2/NETA (last search on 8 October 2023)

To check the completeness of the study pool:

- search in trial registries for relugolix/E2/NETA (last search on 5 December 2023); see Appendix A of the full report for search strategies

The check of completeness of the study pool revealed no relevant study for either research question 1 or research question 2 comparing relugolix/E2/NETA with the ACT defined by the G-BA in women of reproductive age with endometriosis who have already been treated with medication or surgery.

As described in Chapter I 2, the company deviated from the G-BA's specification and instead cited the individualized treatment as the ACT. The company identified the RCTs SPIRIT 1 [6] and SPIRIT 2 [7] that it considers relevant for the comparison of relugolix + E2/NETA with placebo. With these 2 RCTs, however, the company did not present suitable data for the benefit assessment - neither compared to the comparator therapy selected by the company nor compared to the ACT specified by the G-BA. This is justified below.

Evidence provided by the company

SPIRIT 1 and SPIRIT 2 studies

The studies SPIRIT 1 and SPIRIT 2 have an identical study design (so-called twin studies) and are described jointly below.

The studies SPIRIT 1 and SPIRIT 2 are double-blind RCTs comparing relugolix + E2/NETA (free combination) with placebo.

Premenopausal women from 18 up to 50 years inclusively with moderate to severe endometriosis pain were included. Prior endometriosis therapy with medication or surgery was not an inclusion criterion.

In the SPIRIT 1 study, 638 patients and in the SPIRIT 2 study, 623 patients were randomly assigned in a 1:1:1 ratio to one of the following 3 study arms: a) relugolix 40 mg + E2/NETA 1 mg/0.5 mg, b) relugolix 40 mg + E2/NETA 1 mg/0.5 mg (delayed) or c) placebo. In the study arm with delayed administration of E2/NETA, patients received a 12-week relugolix monotherapy followed by 12 weeks of relugolix in combination with E2/NETA. As relugolix monotherapy is not covered by the marketing authorisation for the present therapeutic indication, this study arm is not considered further by the company in the dossier. This approach is appropriate.

In both studies, the use of relugolix was largely in compliance with the requirements of the Summary of Product Characteristics [4]. A free combination of 1 tablet of relugolix 40 mg and 1 capsule of E2/NETA 1 mg/0.5 mg was used instead of the approved fixed combination (1 film-coated tablet of relugolix/E2/NETA [40 mg/1 mg/0 5 mg]) [4]. As described in dossier assessment A21-112 [8], the bioequivalence of the fixed combination and the free combination was demonstrated in the context of the initial marketing authorisation [9] on the basis of study MVT-601-042.

Both studies comprise a single-blind run-in phase of 35 to 70 days, a double-blind, randomized treatment phase of 24 weeks and a subsequent safety follow-up visit (approx. 30 days after the last dose of the study medication). This safety follow-up visit is not required for patients who participated in a single-arm, open-label extension study (Study MVT-601-3103 [10]) following the 24-week treatment phase.

In both studies, the use of level 1 and level 2 analgesics defined in the study protocol as rescue medication were permitted as concomitant treatment during the course of the study.

Co-primary outcomes of the SPIRIT 1 and SPIRIT 2 studies are the proportion of patients with a clinically relevant reduction in dysmenorrhoea at week 24 compared to baseline without an increase in analgesic consumption and the proportion of patients with a clinically relevant reduction in non-menstrual pelvic pain at week 24 compared to baseline without an increase in analgesic consumption. Patient-relevant secondary outcomes in both studies were overall survival as well as outcomes on morbidity, health-related quality of life, and side effects.

For the assessment of added benefit, the company presented a meta-analysis of the RCTs SPIRIT 1 and SPIRIT 2 (relugolix + E2/NETA: N = 418 vs. placebo: N = 416).

Assessment of the evidence presented by the company

Failure of SPIRIT 1 and SPIRIT 2 studies to implement the G-BA's specifications regarding patient population and ACT

The company's dossier examined only 1 research question under which it jointly analysed all patients in the present therapeutic indication. The data presented by the company are not

suitable for assessing the added benefit of relugolix/E2/NETA compared with the ACT in the 2 research questions of the G-BA.

Regardless, the G-BA's ACT was not implemented in the respective placebo arm of the two studies with the administered concomitant therapy in both research questions. The G-BA specified dienogest as the ACT for research question 1 (patients for whom treatment with dienogest is an option) and GnRH analogues for research question 2 (patients for whom treatment with dienogest is no [longer] an option). However, the administration of both progestogens (such as dienogest) and GnRH analogues (research question 2) was prohibited in both studies. In all study arms, patients only received rescue medication as concomitant treatment as required to relieve endometriosis-associated pain with specific level 1 and level 2 analgesics permitted under the study plan. Thus, both studies cannot answer the research questions on the benefit assessment of relugolix/E2/NETA.

The comparator therapy specified by the company was not implemented in the SPIRIT 1 and SPIRIT 2 studies.

As described in Chapter I 2, the company deviated from the definition of the G-BA by naming an individualized treatment with a choice of analgesics, GnRH receptor agonists and invasive treatment options as comparator therapy for the entire target population in the present therapeutic indication, but with the 2 RCTs SPIRIT 1 and SPIRIT 2 it did not present any suitable studies for an adequate comparison of relugolix/E2/NETA with the comparator therapy chosen by it. In both RCTs, neither surgical treatment of endometriosis nor the use of GnRH analogues was permitted. The company's argument in Module 4 B of the full dossier that a comparison with the therapy option level 1 and level 2 analgesics in the context of a single-comparator study is justified for the implementation of individualized treatment was assessed as inappropriate.

According to the recommendation of the European Society of Human Reproduction and Embryology (ESHRE) guideline, non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics - alone or in combination with other treatment options - can be considered to reduce endometriosis-related pain [11]. However, according to the written participation of scientific and medical associations in determining the ACT [5], surgical and hormonal therapies are the focus of care for women with moderate to severe endometriosis pain; symptom-oriented pain therapy can be considered for patients with chronic pain both in the case of insufficient pain reduction through surgical or hormonal therapy and in the case of intolerance and/or contraindications to surgical or hormonal therapy [3,5]. Since treatment with relugolix/E2/NETA corresponds to a therapy approach with medication or surgery, it is assumed that (renewed) hormonal therapy to induce therapeutic amenorrhoea is an option for patients in the present therapeutic indication. Therefore, the sole administration of analgesics for the treatment of pain is not an adequate therapy for this patient population.

With respect to both studies, 542 of 834 (65%) patients had not undergone prior hormonal therapy, meaning that in principle they would have been candidates for treatment with dienogest. Of 292 patients who had undergone prior hormonal therapy, 167 (57%) had already received treatment with dienogest, meaning that dienogest treatment was no longer a treatment option for them. This information on prior therapy contradicts the company's argumentation described in Chapter I 2 that all patients with endometriosis would only be eligible for treatment with relugolix/E2/NETA after treatment failure or insufficient response to treatment with dienogest. As only a small proportion of patients in both studies had undergone prior therapy with GnRH analogues (SPIRIT 1: 14 % vs. 13 %; SPIRIT 2: 5 % vs. 5 %), it can be assumed that hormonal treatment with GnRH analogues would still have been an option for the majority of patients.

In summary, by presenting the SPIRIT 1 and SPIRIT 2 studies, the company presented neither suitable studies compared with the comparator therapy selected by it nor compared with the ACT specified by the G-BA in each case.

I 4 Results on added benefit

There are no suitable data available for assessing the added benefit of relugolix/estradiol/NETA compared to the ACT for the symptomatic treatment of endometriosis in women of reproductive age who have already been treated with medication or surgery. There is no hint of added benefit of relugolix/E2/NETA in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven for either of them.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of relugolix/E2/NETA in comparison with the ACT.

Table 5: Relugolix/E2/NETA – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Symptomatic treatment of endometriosis in adult women of reproductive age who have already been treated with medication or surgery and who are candidates for treatment with dienogest [b]	Dienogest[c]	Added benefit not proven
2	Symptomatic treatment of adult women of reproductive age with endometriosis who have already been treated with medication or surgery and who are no (longer) candidates for treatment with dienogest[b]	GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin)[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that for patients with endometriosis who are candidates for treatment with relugolix/E2/NETA, invasive treatment options are not considered at the current treatment time.
c. Adequate pain therapy should be offered in both study arms.

ACT: appropriate comparator therapy; E2: estradiol; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; NETA: norethisterone acetate

The assessment described above deviates from that by the company, which derived proof of a major added benefit of relugolix/E2/NETA for the entire target population based on the SPIRIT 1 and SPIRIT 2 studies.

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: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Leitlinienprogramm Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe, Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe. S2k-Leitlinie Diagnostik und Therapie der Endometriose; Version 4.0 [online]. 2020 [Accessed: 09.01.2024]. URL: https://register.awmf.org/assets/guidelines/015-045l_S2k_Diagnostik_Therapie_Endometriose_2020-09.pdf.

4. Gedeon Richter. Ryeqo 40 mg/1 mg/0,5 mg Filmtabletten [online]. 2023 [Accessed: 09.01.2024]. URL: https://www.fachinfo.de.

5. Gemeinsamer Bundesausschuss. Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie und Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V und Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V; Vorgang: 2022-B-296 Relugolix / Estradiol / Norethisteronacetat. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1019/#zweckmaessige-vergleichstherapie in the document "Informationen zur zweckmäßigen Vergleichstherapie"].

6. Myovant Sciences. SPIRIT 1: Efficacy and Safety Study of Relugolix in Women With Endometriosis-Associated Pain [online]. [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT03204318.

7. Myovant Sciences. SPIRIT 2: Efficacy and Safety Study of Relugolix in Women With Endometriosis-Associated Pain [online]. [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT03204331.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Relugolix/Estradiol/Norethisteronacetat (Uterusmyome) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 12.01.2024]. URL: https://www.iqwig.de/download/a21-112_relugolix-estradiol-norethisteronacetat_nutzenbewertung-35a-sgb-v_v1-1.pdf.

9. European Medicines Agency. Ryeqo; CHMP assessment report [online]. 2021 [Accessed: 09.01.2024]. URL: https://www.ema.europa.eu/documents/assessment-report/ryeqo-epar-public-assessment-report_en.pdf.

10. Myovant Sciences. SPIRIT EXTENSION: Efficacy and Safety Extension Study of Relugolix in Women With Endometriosis-Associated Pain [online]. [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT03654274.

11. ESHRE Endometriosis Guideline Development Group. Endometriosis; Guideline of European Society of Human Reproduction and Embryology [online]. 2022 [Accessed: 09.01.2024]. URL: https://www.eshre.eu/-/media/sitecore-files/Guidelines/Endometriosis/ESHRE-GUIDELINE-ENDOMETRIOSIS-2022_2.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-117.html.