Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Relugolix/ Estradiol/ Norethisterone acetate (uterine fibroid)

of 17 February 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first submission on the market of the combination of active ingredients relugolix / estradiol / norethisterone acetate in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 27 August 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 December 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of relugolix / estradiol / norethisterone acetate compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared

by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of relugolix / estradiol / norethisterone acetate.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Relugolix/ Estradiol/ Norethisterone acetate (Ryeqo) according to the product information

Ryeqo is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Therapeutic indication of the resolution (resolution of 17.02.2022):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Adult women of reproductive age with moderate to severe symptoms of uterine fibroids:</u>

Appropriate comparator therapy for relugolix/E2/NETA:

- Patient-individual therapy depending on the type and severity of the symptoms as well as the burden of the symptoms on the patient, selecting from:
  - monitoring wait-and-see approach
  - a symptom-oriented treatment:
    - progestogens under consideration of the respective authorisation status (for patients for whom symptomatic treatment of prolonged and/or heavy menstruation (menorrhagia, hypermenorrhoea) is sufficient)
    - ulipristal acetate (for patients who have not yet reached menopause and for whom uterine fibroid embolisation and/or surgery are not suitable or have failed)
  - invasive treatment options

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to relugolix/E2/NETA, GnRH analogues and the progesterone receptor antagonist ulipristal acetate are approved for the treatment of symptomatic uterine fibroids, and progestogens and tranexamic acid for the symptomatic treatment of heavy menstrual bleeding.

on 2. Non-medicinal treatment options include invasive procedures such as hysterectomy, myomectomy or (percutaneous transcatheter) embolisation, but these are not a treatment option for all patients. It should be noted that percutaneous transcatheter embolisation can only be performed in an inpatient setting.

on 3. There are no resolutions approved on the benefit assessment of medicinal products according to Section 35a SGB V. In accordance with Section 137h SGB V, an assessment of the method "Ultrasound-guided high-intensity focused ultrasound for the treatment of leiomyomas of the uterus" was carried out. The benefit of the method was deemed not yet sufficiently proven in a resolution of 16 March 2017.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

The finding of "uterine fibroid" alone does not constitute a disease requiring treatment. The indication for treatment is based on the type and severity of the symptoms and the burden the symptoms place on the patient.

If individual symptoms are in the foreground, symptomatic treatment may be sufficient. Invasive procedures such as hysterectomy, myomectomy and uterine artery embolisa-

tion, on the other hand, can represent a curative approach in the therapeutic indication, depending on the location, size and complexity of the fibroids. If family planning has not yet been completed, however, hysterectomy is not an option. Overall, invasive procedures are associated with possible procedure-associated complications and risks (such as impaired fertility in the case of myomectomy) and are not an option for all patients. It should also be taken into account that organ-preserving invasive procedures may require repeated treatments.

In addition to symptomatic or invasive treatment, monitoring wait-and-see approach is an option for patients whose symptoms are only mild to moderate and whose subjective suffering allows this. This also applies to women for whom both invasive and symptom-oriented therapy are out of the question for medical and/or personal reasons (e.g., family planning). Patients should be able to receive supportive measures such as analgesics and iron supplementation if needed.

Since the need for treatment in the present therapeutic indication is defined by the symptomatology, active ingredients that are approved for this purpose and for which there is no fundamental contraindication for use in the presence of uterine fibroids can be considered for symptomatic treatment.

The progestogens chlormadinone and levonorgestrel (as a component of an intrauterine system) are generally approved for the treatment of hypermenorrhoea in Germany. According to the product information, congenital or acquired malformations of the uterus, including uterine fibroids, if they deform the uterine cavity, are contraindications for the levonorgestrel intrauterine pessary. Accordingly, treatment can also be given for uterine fibroids, as long as these do not deform the cavum uteri. The chlormadinone product information states that patients should be closely monitored if leiomyomas (uterine fibroids) are present or have previously been present or have worsened during pregnancy or previous hormone treatment.

Even taking into account the assumption that progestogens are contraindicated for a (predominant) part of the patients covered by the therapeutic indication, progestogens represent a possible appropriate comparator therapy option for patients for whom symptomatic treatment of prolonged and/or heavy menstruation is sufficient and for whom progestogens can be considered as symptomatic treatment, taking into account the respective authorisation status.

Ulipristal acetate is only approved for a very limited group of patients due to an increased risk of liver damage (premenopausal women with uterine fibroids for whom there are no other treatment options left; i.e., uterine fibroid embolisation and/or surgical interventions are not suitable or have failed). However, taking into account the lack of alternatives and the corresponding level of suffering, ulipristal acetate may be an option in the present therapeutic indication in individual cases.

Gonadotropin releasing hormone agonists (GnRH agonists), which are only approved for the preoperative situation, and tranexamic acid, which is primarily used as an acute therapy for heavy bleeding, are not considered as appropriate comparator therapy in the present indication.

In summary, for adult women in reproductive age with moderate to severe symptoms of uterine fibroids, a patient-individual therapy depending on the type and severity of the symptoms as well as the patient's burden of the symptoms, selecting monitoring wait-and-see approach, symptom-oriented treatment (ulipristal acetate and progestogens taking into account the respective authorisation status) and invasive treatment options, is determined as the appropriate comparator therapy in the present indication.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of relugolix / estradiol / norethisterone acetate is assessed as follows:

a) For adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited, there is a hint of considerable additional benefit for relugolix/E2/NETA.

b) For adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited the additional benefit is not proven.

Justification:

For the present benefit assessment procedure according to Section 35a SGB V, the pharmaceutical company submitted the two LIBERTY 1 and LIBERTY 2 studies (hereinafter referred to as LIBERTY 1/2) with identical study design. These are randomised, double-blind, multicentre phase III studies comparing the free combination of relugolix and estradiol (E2)/norethisterone acetate (NETA) with placebo over 24 weeks. Premenopausal women with uterine fibroids and associated hypermenorrhoea were included. Patients who were scheduled to undergo invasive procedures for the treatment of uterine fibroids within 6 months of study enrolment or who had osteoporosis or were at increased risk for it were excluded from the study.

Participants in the two studies (LIBERTY 1 study n=388; LIBERTY 2 study n=382) received either continuous treatment with relugolix + E2/NETA or placebo, or E2/NETA delayed after 12 weeks of treatment with relugolix. In addition to the study medication, the patients in both study arms had the option of taking analgesics for the treatment of uterine fibroid-associated pain and iron supplements for iron deficiency anaemia.

The use of the combined treatment of relugolix+E2/NETA was largely in accordance with the product information of the fixed medicinal product. Since the bioequivalence of the fixed combination and the free combination was demonstrated in the context of the marketing authorisation, the results of the LIBERTY studies with the free combination can be used for the benefit assessment of the fixed combination. The delayed administration of E2/NETA, on the other hand, does not correspond to the information in the marketing authorisation, so that these study arms are not suitable for the present benefit assessment.

Endpoints collected included menstrual blood loss (MBL) and pain, as well as other endpoints on morbidity, health-related quality of life and side effects.

Implementation of the appropriate comparator therapy

Since in the two studies presented, LIBERTY 1/2, in the comparator arm, in addition to placebo, concomitant medication with analgesics as well as iron supplementation was possible, this is considered a sufficient approximation to monitoring wait-and-see approach. However, monitoring wait-and-see approach is only one of the possible therapy options to be chosen patient-individual within the specific appropriate comparator therapy. A complete implementation of

the appropriate comparator therapy in the sense of a multicomparator study including invasive and symptom-oriented treatment options is therefore not available.

On the basis of the available studies, the benefit assessment can therefore only use results from a sub-population of patients for whom, in the context of the appropriate comparator therapy, monitoring wait-and-see approach is patient-individual best suited.

Monitoring wait-and-see approach can be considered especially for women who have less pronounced symptomatology and whose subjective suffering allows this.

However, the LIBERTY 1/2 study participants had severe hypermenorrhoea at start of study (average MBL volume of about 210 to 250 ml per cycle) and suffered from other symptoms such as uterine fibroid-related pain (91%), feelings of tension and pressure in the pelvic area (93%) or fatigue (95%). Therefore, as will be described in more detail below, there is uncertainty as to whether monitoring wait-and-see approach was patient-individual the best for the study participants in LIBERTY 1/2.

Even if it is assumed that the patients consciously refrained from invasive procedures as a therapy option for the period of the study and that there was no obviously compelling medical indication, for a certain proportion of included patients, especially for those with high blood loss during menstruation, an invasive therapy option could have been patient-individual better suited than monitoring wait-and-see approach with described concomitant medication. The situation is similar with the medicinal options that could have been a suitable treatment for individual patients: Ulipristal acetate for study participants who refuse an invasive procedure or have already had a previous procedure due to uterine fibroids, and progestogens for patients without corresponding contraindications, for whom the treatment of bleeding symptomatology was the main focus.

At the same time, for some patients, neither invasive interventions nor ulipristal acetate or progestogens are an individually adequate option despite pronounced symptomatology and high levels of suffering, e.g., due to contraindications and the limited indications. The proportion of these patients in the LIBERTY 1/2 studies cannot be deduced from the available information.

Overall, the LIBERTY 1 and LIBERTY 2 studies are used despite the uncertainty described regarding the implementation of the appropriate comparator therapy.

Distribution of the patient population

As already explained, for the benefit assessment, only results from patients are available for whom, in the context of the appropriate comparator therapy, monitoring wait-and-see approach is patient-individual best suited. Therefore, the G-BA considers a division of the patient population according to the suitability for "monitoring wait-and-see approach" to be appropriate. Consequently, the appropriate comparator therapy for patients, for whom monitoring wait-and-see approach is most appropriate, consists of monitoring wait-and-see approach, and for patients, for whom monitoring wait-and-see approach is patient-individual not most appropriate, it consists of patient-individual therapy with a choice of symptom-based treatments or invasive treatment options.

a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited

Extent and probability of the additional benefit

Mortality

There were no deaths in either study during the course of the studies.

Morbidity

Menstrual blood loss assessed via "Confirmed clinically relevant reduction in MBL-volume" and "confirmed amenorrhoea"

To assess the impact of relugolix/E2/NETA on the core symptomatology hypermenorrhoea, the confirmed clinically relevant reduction in menstrual blood loss volume (referred to in the dossier as permanent normalisation of MBL-volume) and confirmed amenorrhoea are used as patient-relevant endpoints. Confirmed clinically relevant reduction in MBL volume was operationalised as MBL volume of < 80 ml and at least a 50 %-reduction in baseline MBL volume measured by the alkaline haematin method that had persisted at least since the previous evaluation time point and until the end of the study.

In the meta-analysis of the LIBERTY 1/2 studies, there was a statistically significant difference in favour of relugolix + E2/NETA for this endpoint. This is consistent with the results on confirmed amenorrhoea (amenorrhoea that existed at least since the previous evaluation time and until the end of the study). A majority of patients who had heavy menstrual bleeding at the start of the study had no bleeding at the end of the study in the relugolix E2/NETA arm. This represents a significant improvement in the core symptomatology.

Pain (NRS)

In the LIBERTY 1/2 studies, patients rated the maximum intensity of their uterine fibroid-related pain daily using an 11-point numerical rating scale (NRS). A value of 0 corresponds to no pain and a value of 10 to the worst pain imaginable. For the benefit assessment, the operationalisation "reduction of the maximum NRS-score within the last 35 days before a visit" is used based on the entire study population and the change compared to the start of the study is considered in relation to all visits during the course of the study.

In the meta-analysis of the studies, there was a statistically significant difference in the endpoint to the benefit of relugolix + E2/NETA. The 95% confidence interval of the standardised mean difference is completely outside the irrelevance range of -0.2 to 0.2, so that a clinically relevant difference is assumed.

Symptomatology (Symptom Severity Scale of the UFS-QoL)

The Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QoL) is a valid, disease-specific instrument to assess uterine fibroid-associated symptoms and health-related quality of life. The questionnaire comprises 37 items, all of which are asked using a 5-point Likert scale. All scales are transformed to values from 0 to 100. The Symptom Severity Scale, which is presented under the endpoint category morbidity, comprises 8 items that record typical symptoms in the therapeutic indication, such as menstrual cramps, a feeling of tension and pressure in the pelvic area, fatigue and increased urinary frequency.

In the meta-analyses based on the responder analyses submitted during the written statement procedure with a clinical relevance threshold of 15%, there is a statistically significant difference in the benefit of relugolix/E2/NETA compared to monitoring wait-and-see approach for this endpoint.

However, it is unclear whether effect modifications are present, particularly due to disease severity (MBL volume < 225 ml / ≥ 225 ml]), as no subgroup analyses for relevant subgroup features were subsequently submitted for the responder analyses presented.

Health status (EQ-5D VAS)

Health status was assessed in the LIBERTY 1/2 study using the visual analogue scale of the EuroQoL-5 dimensions (EQ 5D). There was no statistically significant difference between the treatment groups for the changes between the start of the study and week 24 in the meta-analysis.

Quality of life

For the assessment of health-related quality of life, the total score of the already mentioned questionnaire UFS-QoL is used, which consists of 6 subscales (Concern, Activities, Energy/ mood, Control, Self-conciousness and Sexual function).

In the meta-analyses based on the responder analyses submitted during the written statement procedure with a clinical relevance threshold of 15%, there is a statistically significant difference in the benefit of relugolix/E2/NETA compared to monitoring wait-and-see approach for this endpoint.

As with the endpoint symptomatology, no subgroup analyses are available here that would allow conclusions to be drawn about effect modifications due to disease severity in particular.

Side effects

For the present benefit assessment, the overall rates of adverse events (AEs) and serious adverse events (SAEs) are used. In the meta-analysis of the studies, there were no statistically significant differences between the treatment groups for the endpoints SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs.

Vasomotor and skeletal events were considered as specific AEs. Again, there were no statistically significant differences in the meta-analysis between the study arms.

With regard to skeletal-related events, however, the significance is limited, as the duration of the LIBERTY studies with 24 weeks is too short for a sufficient assessment of skeletal-related events and comparative long-term data would be necessary for this.

Overall assessment

For the treatment of adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited, results on mortality, morbidity, quality of life and side effects are meta-analytically summarised on the basis of the two pivotal phase III studies LIBERTY 1/2.

In the endpoint category mortality, no deaths occurred in the two studies.

In the category of morbidity, there are statistically significant, clinically relevant advantages in favour of relugolix/E2/NETA for the patient-relevant endpoints menstrual blood loss (confirmed clinically relevant reduction in MBL volume, confirmed amenorrhoea), pain and fibroid-associated symptomatology (Symptom Severity Scale of the UFS-QoL). There was no statistically significant change in health status for relugolix/E2/NETA compared to monitoring wait-and-see approach.

For health-related quality of life, there is an advantage for relugolix/E2/NETA based on the UFS-QoL total score.

Neither advantages nor disadvantages are available for the endpoint category side effects. However, the duration of the LIBERTY studies of 24 weeks is too short for a sufficient evaluation of skeletal-related events.

In summary, the existing statistically significant and clinically relevant advantages of relugolix/E2/NETA over monitoring wait-and-see approach with regard to the endpoints of menstrual blood loss (confirmed clinically relevant reduction in MBL volume, confirmed amenorrhoea), symptomatology (Symptom Severity Scale of the UFS-QoL) and health-related quality of life (total score of the UFS QoL) are classified as considerable in their magnitude in the overall assessment. The advantages in the pain endpoint support this assessment.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the randomised, controlled, multicentre, phase III LIBERTY 1/2 studies, which investigated the efficacy and safety of relugolix/E2/NETA versus monitoring wait-and-see approach.

The cross-endpoint risk of bias is rated as low for both studies. The risk of bias in the results of all relevant endpoints is high in both studies, with the exception of the endpoint discontinuation due to AEs. For the endpoint discontinuation due to AEs, there is a reduced reliability of data with low risk of bias.

However, the uncertainties in the implementation of the appropriate comparator therapy are primarily used to assess the reliability of data. It is unclear whether for the study participants in LIBERTY 1/2, monitoring wait-and-see approach was patient-individual the most suitable treatment option or whether other therapies of the appropriate comparator therapy would have been more suitable. In the overall assessment the result is a hint for an additional benefit with regard to reliability of data.

b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited

The pharmaceutical company has not submitted any study data on Relugolix/E2/NETA versus the appropriate comparator therapy. Thus, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerts the benefit assessment of the new medicinal product “Ryeqo” with the combination of active ingredients relugolix, estradiol and norethisterone

acetate (Relugolix/E2/NETA). The medicinal product is used in adult women in reproductive age for the treatment of moderate to severe symptoms of uterine fibroids.

The G-BA determined the appropriate comparator therapy to be a patient-individual therapy selecting monitoring wait-and-see approach, symptom-oriented treatment and invasive treatment options.

The randomised controlled LIBERTY 1 and LIBERTY 2 studies were presented, comparing relugolix/E2/NETA versus placebo over 24 weeks. A study versus the different options of the appropriate comparator therapy is not available.

The administration of placebo in conjunction with the permitted concomitant medication is considered a sufficient approximation to monitoring wait-and-see approach.

Since, on the basis of the available studies, results from a sub-population of patients can be used for whom, in the context of the appropriate comparator therapy, monitoring wait-and-see approach is patient-individual best suited, a distinction is made between two patient groups: Adult women in reproductive age with moderate to severe symptoms of uterine fibroids for whom a) monitoring wait-and-see approach is patient-individual best suited and b) monitoring wait-and-see approach is patient-individual not best suited.

a) Adult women in reproductive age with moderate to severe symptoms of uterine fibroids, for whom monitoring wait-and-see approach is patient-individual best suited

There were no deaths in the LIBERTY 1/2 studies. In the morbidity category, there were statistically significant, clinically relevant benefits to the advantage of relugolix/E2/NETA for the patient-relevant endpoints of menstrual blood loss (confirmed clinically relevant reduction in MBL volume, confirmed amenorrhoea), pain and fibroid-associated symptoms (Symptom Severity Scale of the UFS-QoL). There was no statistically significant change in health status.

For health-related quality of life, there is an advantage for relugolix/E2/NETA based on the UFS-QoL total score.

There are neither advantages nor disadvantages to the side effects.

Uncertainties exist in particular with regard to the implementation of the appropriate comparator therapy. Due to the severity of the symptoms at the start of the study, it is unclear whether monitoring wait-and-see approach was patient-individually the most appropriate treatment option or whether other treatment options of the appropriate comparator therapy would have been more suitable.

In the overall assessment, a hint of considerable additional benefit is determined.

b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited

No study data is available for this patient group. An additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information provided by the pharmaceutical company and the IQWiG assessment (A21-112). No information is available in the dossier on the percentage of patient populations a) and b) in the target population. Therefore, the information on the total population is taken into account.

Overall, the number of patients in the SHI target population estimated by the pharmaceutical company tends to be underestimated, taking into account existing uncertainties for the lower limit. This is based in particular on the fact that only patients who received medicinal therapy and for whom a prescribed therapy was linked to the diagnosis were taken into account. In addition, female patients under 30 years of age were excluded.

The upper limit given is subject to uncertainties as no outpatient procedures are taken into account. In addition, an overestimation is assumed, as patients may be included who did not receive one of the listed therapies due to moderate to severe symptoms of uterine fibroids. In addition, double counting is possible due to the addition of patients with invasive procedure and patients with prescribed therapy on the day of diagnosis.

In addition to the existing uncertainties, the estimated number of patients in the therapeutic indication does not take into account that relugolix/E2/NETA cannot be used in patients with a current desire to have children due to its contraceptive effect.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Ryeqo (active ingredient: relugolix / estradiol / norethisterone acetate) at the following publicly accessible link (last access: 6 December 2021):
https://www.ema.europa.eu/en/documents/product-information/ryeqo-epar-product-information_en.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The use of ulipristal acetate is limited to 4 treatment intervals of up to 3 months. For the cost presentation, a treatment interval with a maximum duration of 3 months is shown as an example. The intrauterine pessary with the active ingredient levonorgestrel may remain in the body for up to 5 years in the indication hypermenorrhoea, according to the product information (Mirena last revised September 2021).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Relugolix / estradiol / norethisterone acetate	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited				
Monitoring wait-and-see approach	-			
b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited				
Symptom-oriented treatment				
Chlormadinone	on day 16 - 25 of a cycle	13	10	130
Levonorgestrel	1 x for up to 5 years	1	1	1
Ulipristal acetate	1 x daily for up to three months[2]	91.2	1	91.2
Invasive treatment options				
Hysterectomy	once		3.5 - 4.3 (average length of stay)	
Myomectomy	once[3]		2.7 - 3.6 (average length of stay)	
Percutaneous transluminal angioplasty	once[3]		4.5 (average length of stay)	

[2] The treatment interval of up to three months can be carried out up to four times.

[3] Treatment can be repeated if necessary.

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Relugolix / estradiol / norethisterone acetate	40 mg/1 mg/0.5 mg	40 mg/1 mg/0.5 mg	1 x 40 mg/1 mg/0.5 mg	365	365 x 40 mg/1 mg/0.5 mg
Appropriate comparator therapy					
a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited					
Monitoring wait-and-see approach	-				
b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited					
Symptom-oriented treatment					
Chlormadinone	2 mg -	2 mg -	1 x 2 mg -	130.0	130 x 2 mg -
	4 mg	4 mg	2 x 2 mg		260 x 2 mg
Levonorgestrel Intrauterine pessary	20 µg	20 µg	20 µg	1	1 intrauterine pessary
Ulipristal acetate	5 mg	5 mg	1 x 5 mg	91.2	91.2 x 5 mg
Invasive treatment options					
Hysterectomy	-				
Myomectomy	-				
Percutaneous transluminal angioplasty	-				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Relugolix / estradiol / norethisterone acetate	84 FCT	€ 295.75	€ 1.77	€ 15.75	€ 278.23
Appropriate comparator therapy					
a) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual best suited					
Monitoring wait-and-see approach	-				
b) Adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individual not best suited					
Chlormadinone	100 TAB	€ 35.45	€ 1.77	€ 1.34	€ 32.34
Levonorgestrel	1 IUP	€ 128.44	€ 1.77	€ 14.83	€ 111.84
Ulipristal acetate	84 TAB	€ 576.80	€ 1.77	€ 31.31	€ 543.72
Abbreviations: FCT = film-coated tablets; IUP = intrauterine pessary; TAB = tablets					

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Costs of invasive treatment methods

Designation of the therapy	DRG	Mean length of stay (days)	Basic fee	Nursing fee[4]	Case flat fee
Hysterectomy	N21A[5]	4.3	€ 4,456.35	€ 660.35	€ 5,116.7[6]
Hysterectomy	N07A[7]	3.5	€ 3,278.48	€ 549.40	€3,827.88
Myomectomy	N23Z[8]	3.6	€ 3,987.85	€ 583.72	€ 4,571.57
Myomectomy	N25Z[9]	2.7	€ 2,799.73	€ 463.35	€ 3,263.08
Percutaneous transluminal angioplasty	N06Z[10]	4.5	€ 4,006.59	€ 647.45	€ 4,654.04

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

There are additional costs for inserting and removing the intrauterine pessary with the active ingredient levonorgestrel. Since the intrauterine pessary with the active ingredient levonorgestrel can remain in the body for up to 5 years in the indication hypermenorrhoea according to the product information (Mirena, last revised September 2021), only the costs for insertion are taken into account as additional costs for the first year.

[4] The average length of stay was rounded up to whole days for the calculation of the nursing fee.

[5] An operation and procedure code from the range 5-683.0 - 5-683-3 (except 5683.01 and 5683.21), diagnosis code D25.- (ICD-10-GM 2022), case flat fee N21A (G-DRG 2022).

[6] Surgery and procedure code 5683.01 or 5683.21, diagnosis code D25 (ICD-10-GM 2022), case flat fee N21A (G-DRG 2022).

[7] An operation and procedure code from the range 5-683.0 - 5-683-3 (except 5683.01 and 5683.21), 5-681.81 or 5-681.82, diagnosis code D25.- (ICD-10-GM 2022), case flat fee N21A (G-DRG 2022).

[8] An operation and procedure code from the range 5-681.90- 5-681.96 (except 5681.93), 5-681.80 or 5-681.85 diagnosis code D25.- (ICD-10-GM 2022), case flat fee N23Z (G-DRG 2022).

[9] Surgery and procedure code 5681.93, 5-681.86 or 5-681.83, diagnosis code D25 (ICD-10-GM 2022), case flat fee N23Z (G-DRG 2022).

[10] Surgery and procedure codes 8-836.kh, 8-83b.1 ff. and, if applicable, additional code 8-83b.k, diagnosis code D25.- (ICD-10-GM 2022), case flat fee N06Z (G-DRG 2022).

Designation of the therapy	Designation of the service	Cost per unit	Number per patient per year	Cost per Patient per year
Appropriate comparator therapy				
Levonorgestrel	Insertion of a pessary, intrauterine, because of a disease GOP 08330	€ 6.99	1	€ 6.99

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 22 December 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 February 2021.

On 27 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of relugolix / estradiol / norethisterone acetate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 31 August 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient relugolix / estradiol / norethisterone acetate.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

By letter dated 11 January 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 28 January 2022.

On 28 January 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 28 January 2022 replaces version 1.0 of the dossier assessment dated 29 November 2021. The evaluation result was not affected by the changes in version 1.1 compared to version 1.0.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella

organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	22 December 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	23 February 2021	New determination of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 January 2022 25 January 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken-