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 (new therapeutic indication: endometriosis, after medical or surgical treatment)

of 16 May 2024

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 combination of active ingredients relugolix/ estradiol/ norethisterone acetate (Ryeqo) was listed for the first time on 1 September 2021 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 30 October 2023, relugolix/ estradiol/ norethisterone acetate received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 23 November 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the combination of active ingredients relugolix/ estradiol/ norethisterone acetate with the new therapeutic indication "Ryeqo is indicated in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis" in

due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), 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 to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. 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 in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis.

Therapeutic indication of the resolution (resolution of 16.05.2024):

“see approved therapeutic indication”

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Patients of reproductive age with endometriosis with a history of previous medical or surgical treatment; for symptomatic treatment</u>

Appropriate comparator therapy for relugolix/E2/NETA:

- Patient-individual therapy, taking into account previous therapy, possible organ destruction and the localisation and extent of the endometriosis lesions, with selection of
    - Dienogest

[1] General Methods, version 7.0 of 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- GnRH analogues (goserelin or buserelin or leuprorelin or triptorelin or nafarelin)
- Surgical measures

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to the combination of active ingredients to be assessed relugolix/ E2/ NETA, GnRH analogues (goserelin, buserelin, leuprorelin, triptorelin, nafarelin) and the progestin dienogest are approved explicitly for the treatment of endometriosis.

on 2. Non-medicinal treatment options include surgical procedures such as complete or partial resection of the endometriosis lesions, ablative procedures to remove the lesions, a hysterectomy or an ovarian cystectomy.

on 3. In the present therapeutic indication, there are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients 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 endometriosis of the uterus" was carried out. By resolution of 16 March 2017, it was determined that the method does not offer the potential of a necessary alternative treatment.

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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

Endometriosis can be accompanied by various symptoms. In addition to dysmenorrhoea, patients may also suffer from dysuria, dyschezia, dyspareunia and/or other non-specific symptoms such as back pain, headaches, nausea and lower abdominal pain. Since the present therapeutic indication comprises the symptomatic treatment of endometriosis, active ingredients that are approved for the various symptoms and for which there is no fundamental contraindication for use in endometriosis (e.g. pain) are also considered.

The aggregated evidence shows that hormonal treatments and/or surgical resection of endometriosis lesions are used to treat patients with symptomatic endometriosis. Analgesics are also used for persistent pain.

Even if analgesics are used to treat endometriosis-associated pain, the G-BA does not consider them to be an adequate comparison to relugolix/ E2/ NETA, as it is assumed that patients for whom treatment with analgesics alone is best suited patient-individually are generally not equally suitable for hormonal therapy. However, within the framework of a clinical study, adequate pain therapy should be possible in both study arms. According to the guideline recommendations[2,3], hormonal therapies that can be considered include progestogens, combined oral contraceptives and GnRH analogues. Only the progestogen dienogest and the GnRH analogues goserelin,

[2] German Society of Gynaecology and Obstetrics (DGGG), Austrian Society of Gynaecology and Obstetrics (OEGGG), Swiss Society of Gynaecology and Obstetrics (SGGG). Diagnosis and treatment of endometriosis; S2k guideline, long version, version 4.0 [online]. AWMF registry number: 015-045. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2020. www.awmf.org

[3] European Society of Human Reproduction and Embryology (ESHRE). Endometriosis [online]. Grimbergen (BEL): ESHRE; 2022. www.eshre.eu

buserelin, leuprorelin, triptorelin and nafarelin are approved for the treatment of endometriosis. In addition, the progestogen chlormadinone acetate (CMA) is approved for the treatment of dysmenorrhoea. However, CMA is unsuitable for treatment compliant with the marketing authorisation, as it should be used cyclically in accordance with the requirements in the product information. However, the main principle of hormonal therapy is the induction of therapeutic amenorrhoea, which should be achieved through continuous use.

Guidelines primarily recommend the use of progestogens as hormonal therapy. Although GnRH analogues can also reduce symptoms associated with endometriosis, according to the German S2k guideline they can only be considered as a second-line hormonal therapy following progestogen therapy due to their side effect profile, particularly menopausal conditions and a reduction in bone density. To reduce the side effects, an add-back therapy with a suitable oestrogen-progestogen combination is recommended. Add-back therapy is an off-label application. Only in the case of leuprorelin is it described in the product information that NETA can be used as an add-back therapy and thus the treatment duration can be extended from 6 to up to 12 months. However, NETA is not commercially available as a monopreparation in Germany.

In addition to hormonal/ medicinal therapy, surgical measures can be considered for the treatment of endometriosis-related conditions. The complexity and type of surgical procedures vary depending on the location and extent of the endometriosis lesions. Resection/ excision of the endometrial lesions is usually performed; ablative procedures can also be used in the case of superficial peritoneal infestation. If the desire to have children is complete, a hysterectomy can be performed as an alternative to organ-preserving procedures in the presence of adenomyosis. A complete cystectomy of the endometriomas is recommended for ovarian endometriosis. The decision for or against surgical intervention is different from patient to patient and depends, among other things, on previous therapy as well as the localisation and extent of the endometriosis. In the case of recurrent conditions after a surgical intervention, medicinal therapy is usually recommended prior to surgical therapy.

Overall, for the symptomatic treatment of women of reproductive age with endometriosis who have already undergone medicinal or surgical treatment, a patient-individual therapy selecting from dienogest, GnRH analogues, and surgical measures is established as the appropriate comparator therapy for relugolix/ estradiol/ norethisterone acetate. The selection of the patient-individual treatment option should take into account the previous therapy, possible organ destruction and the localisation and extent of the endometriosis lesions.

As no superiority or inferiority of an active ingredient within the product class of GnRH analogues could be derived on the basis of the evidence, all approved active ingredients (goserelin or buserelin or leuprorelin or triptorelin or nafarelin) are considered equally appropriate therapy options for this product class.

Change of the appropriate comparator therapy

As part of the written statement procedure, scientific-medical societies and clinical experts stated that surgical interventions are of considerable importance in this therapeutic indication, even if they should only be carried out with caution, especially if the endometriosis lesions have previously been surgically removed. If the primarily used dienogest is not tolerated or leads to insufficient therapeutic success, there are only limited therapeutic alternatives to surgical interventions apart from the medicinal

product to be assessed, according to the written statement experts, as GnRH analogues can only be used for a limited period of time.

For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy for relogulix/ estradiol/ norethisterone acetate at the present time.

Accordingly, for the entire target population of the therapeutic indication, i.e. for patients of reproductive age with endometriosis with a history of previous medicinal or surgical treatment, a patient-individual therapy is defined as appropriate comparator therapy for relugolix/ estradiol/ norethisterone acetate, taking into account previous therapy, possible organ destruction and localisation and extent of the endometriosis lesions, selecting dienogest, GnRH analogues and surgical measures. It is no longer necessary to divide the patient groups, as it is assumed that the suitability of each patient for dienogest will be assessed as part of the patient-individual therapy.

The change in the appropriate comparator therapy has no impact on the present benefit assessment.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

For patients of reproductive age with endometriosis with a history of previous medical or surgical treatment (for symptomatic treatment), the additional benefit is not proven.

Justification:

For the present benefit assessment procedure according to Section 35a SGB V, the pharmaceutical company submitted a meta-analysis of the two SPIRIT 1 and SPIRIT 2 studies with identical study design. These are randomised, double-blind studies which compared the efficacy and safety of the free combination of relugolix and estradiol (E2)/ norethisterone acetate (NETA) with placebo over 24 weeks.

Premenopausal women aged between 18 and 50 years with moderate to severe pain from endometriosis were enrolled. A history of previous medicinal or surgical treatment of endometriosis was not an inclusion criterion.

Participants in the two studies (SPIRIT 1 study n = 638; SPIRIT 2 study n = 623) 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 use of defined analgesics (level 1 and 2) as emergency medication was permitted as concomitant treatment during the course of the study.

The use of the continuous 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 SPIRIT 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.

The endpoints collected included the reduction of dysmenorrhoea or non-menstrual pelvic pain without an increase in analgesic consumption as well as other endpoints relating to morbidity, health-related quality of life and side effects.

In both studies, neither the use of the hormonal therapy options dienogest and/or GnRH analogues nor surgical treatment of endometriosis was permitted. The SPIRIT 1 and 2 studies are thus unsuitable for deriving an additional benefit of Relugolix/E2/NETA compared to the appropriate comparator therapy.

In the overall assessment, the additional benefit for patients of reproductive age with a history of previous medicinal or surgical treatment of endometriosis is not proven, as no suitable data are available compared to the determined appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the combination of active ingredients relugolix/ estradiol (E2)/ norethisterone acetate (NETA). The therapeutic indication assessed here is "Ryeqo is indicated in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medicinal or surgical treatment for their endometriosis."

The G-BA determined the appropriate comparator therapy to be a patient-individual therapy, taking into account the previous therapy, possible organ destruction and the localisation and extent of the endometriosis lesions, selecting dienogest, GnRH analogues and surgical measures.

The pharmaceutical company presents a meta-analysis of two randomised, double-blind studies, SPIRIT 1 and SPIRIT 2, comparing the efficacy and safety of the free combination of relugolix and estradiol (E2)/ norethisterone acetate (NETA) with placebo in premenopausal women with moderate to severe pain from endometriosis over 24 weeks.

In both studies, neither the use of the hormonal therapy options dienogest and/or GnRH analogues nor surgical treatment of endometriosis was permitted. The SPIRIT 1 and 2 studies are thus unsuitable for deriving an additional benefit of Relugolix/E2/NETA compared to the appropriate comparator therapy.

In the overall assessment, there are no suitable data versus the determined appropriate comparator therapy. The additional benefit for patients of reproductive age with a history of previous medicinal or surgical treatment of endometriosis is therefore 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 from the dossier assessment of the IQWiG (mandate A23-117). However, the number of patients in the SHI target population stated by the pharmaceutical company overall is uncertain due to both underestimation and overestimation factors. Underestimation factors include the fact that not all patients for whom treatment for endometriosis was prescribed were taken into account, and the operationalisation and transferability of the percentage of pretreated patients with

symptomatic endometriosis is questionable. One of the overestimation factors is that there may have been double counting.

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: 7 May 2024):

https://www.ema.europa.eu/en/documents/product-information/ryeqo-epar-product-information_en.pdf

Treatment with relugolix / estradiol / norethisterone acetate should only be initiated and monitored by doctors experienced in the therapy of endometriosis.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

In this therapeutic indication, endometriosis lesions can occur in different organs and with different degrees of infiltration. Due to the complexity and type of surgical interventions, which vary depending on the location and extent of the endometriosis lesions, the necessary surgical measures must be decided on a patient-individual basis. It is assumed that the patient can undergo some of the surgical measures as an outpatient and some as an inpatient.

Treatment period:

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 varies from patient to patient 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 duration of use of goserelin, triptorelin and nafarelin is limited to 6 months according to the respective product information. The treatment duration for buserelin is limited to a maximum of 9 months; as a rule, 6 months is assumed.

According to the product information, leuprorelin can be used for a maximum of 6 months and can be extended for 1 year in combination with 5 mg norethisterone acetate daily as add-back therapy. As norethisterone acetate is not available as monotherapy in Germany, the use of leuroprorelin is only shown for 6 months.

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	365.0	1	365.0
Appropriate comparator therapy				
Dienogest				
Dienogest	Continuously, 1 x daily	365.0	1	365.0
GnRH analogues				
Buserelin	3 x daily	182 - 274	1	182 - 274
Goserelin	1 x per 28-day cycle	6	1	6
Leuprorelin	1 x every 28 days	6	1	6
	1 x every 3 months	2	1	2
Nafarelin	2 x daily	182	1	182
Triptorelin	1 x per 28-day cycle	6	1	6
Surgical measures				
Different from patient to patient				

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

The (daily) doses in the product information were used as the calculation basis.

Designation of the therapy	Dosage/ application	Dose/ 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Dienogest					
Dienogest	2 mg	2 mg	1 x 2 mg	365	365 x 2 mg
GnRH analogues					
Buserelin	0.15 mg	0.9 mg	6 x 0.15 mg	182 - 274	182 x 0.9 mg - 274 x 0.9 mg
Goserelin	3.6 mg	3.6 mg	1 x 3.6 mg	6	6 x 3.6 mg
Leuprorelin	3.75 mg	3.75 mg	1 x 3.75 mg	6	6 x 3.75 mg
	11.25 mg	11.25 mg	1 x 11.25 mg	2	2 x 11.25 mg
Nafarelin	0.2 mg	0.4 mg	2 x 0.2 mg	182	364 x 0.2 mg
Triptorelin	3.75 mg	3.75 mg	1 x 3.75 mg	6	6 x 3.75 mg
Surgical measures					
Different from patient to patient					

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 consumption. 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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 40 mg/ 1 mg/0.5 mg	84 FCT	€ 283.09	€ 2.00	€ 15.05	€ 266.04
Appropriate comparator therapy					
Dienogest					
Dienogest 2 mg[4]	84 FCT	€ 44.46	€ 2.00	€ 2.62	€ 39.84
GnRH analogues					
Buserelin 0.15 mg	2 NAS	€ 187.40	€ 2.00	€ 9.75	€ 175.65
Goserelin 3.6 mg	3 IMP	€ 632.16	€ 2.00	€ 34.37	€ 595.79
Leuprorelin 3.75 mg	3 SRT/SUS	€ 501.87	€ 2.00	€ 27.16	€ 472.71
Leuprorelin 11.25 mg	2 IMP	€ 730.78	€ 2.00	€ 86.93	€ 641.85
Nafarelin 2 mg	1 NAS	€ 200.44	€ 2.00	€ 12.14	€ 186.30
Triptorelin 3.75 mg	1 PII	€ 224.71	€ 2.00	€ 27.01	€ 195.70
Abbreviations: FCT = film-coated tablets; IMP = implant; NAS = nasal spray; PII = powder for the preparation of a solution for injection or infusion; SRT = sustained release tablet; SUS = suspension					

LAUER-TAXE® last revised: 15 April 2024

Costs of surgical measures:

It should be noted that different billing terms and fees would have to be taken into account in the outpatient sector.

Calculation year	DRG	Average stay [d]	DRG valuation ratio main department	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Appropriate comparator therapy									
Surgical measures									
2024	*Miscellaneous*	–	–	*€ 4210.59*	–		–	–	*Not calculable*

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

[4] Fixed reimbursement rate

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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the

reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients of reproductive age with endometriosis with a history of previous medical or surgical treatment; for symptomatic treatment

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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 21 February 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 23 November 2023, 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 2, sentence 2 VerfO.

By letter dated 29 November 2023 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 28 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

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 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	21 February 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	3 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 April 2024	Conduct of the oral hearing
Working group Section 35a	16 April 2024 29 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

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

Prof. Hecken