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
Linzagolix (uterine fibroid)

of 6 March 2025

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 all 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 start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient linzagolix on 15 September 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 06 September 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 December 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 linzagolix 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, 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 linzagolix.

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 Linzagolix (Yselty) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 06.03.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult women of reproductive age with moderate to severe symptoms of uterine fibroids

Appropriate comparator therapy:

- Individualised therapy with selection of:
  - a symptom-oriented treatment:
    - relugolix/ estradiol/ norethisterone acetate
    - progestogens under consideration of the respective authorisation status (for patients for whom symptomatic treatment of prolonged and/or heavy menstruation (menorrhagia, hypermenorrhoea) is sufficient.)
  - invasive treatment options

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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

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

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.

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

On 1. In addition to linzagolix, relugolix/ estradiol (E2)/ norethisterone acetate (NETA) and GnRH analogues are approved for the treatment of symptomatic uterine fibroids and progestogens (chlormadinone, levonorgestrel) 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. A resolution of 17 February 2022 on relugolix/ E2/ NETA according to Section 35a SGB V is available. 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 therapeutic 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 medicinal treatment may be sufficient. Invasive procedures such as hysterectomy, myomectomy and uterine artery embolisation, 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.

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 also 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 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.

The GnRH antagonist relugolix/ E2/ NETA has recently been explicitly approved for the treatment of moderate to severe symptoms of uterine fibroids. By resolution of 17 February 2022, a hint for a considerable additional benefit of this combination of active ingredients was identified for adult women of reproductive age with moderate to severe symptoms of uterine fibroids for whom monitoring wait-and-see approach is patient-individually best suited. On the contrary, no additional benefit could be derived

for patients for whom monitoring wait-and-see approach is not patient-individually best suited.

In view of the statements made by the clinical experts in the written statement procedure and the very limited availability of medicinal options in the therapeutic indication, it is assumed that relugolix/ E2/ NETA has now assumed relevant significance in medical treatment practice.

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 of reproductive age with moderate to severe symptoms of uterine fibroids, an individualised therapy with a choice of symptom-oriented treatment (relugolix/ E2/ NETA and progestogens in consideration of the respective authorisation status) and invasive treatment options is determined as the appropriate comparator therapy in the present therapeutic indication.

Individualised therapy is based on the assumption that the treating physicians can choose from the various therapy options. The treatment decision is made individually for each subject in this therapeutic indication, especially considering the nature and severity of the symptoms and the burden of the symptoms on the patient.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

Change of the appropriate comparator therapy

Until now, the active ingredient ulipristal acetate was considered a possible therapy option for symptomatic patients with uterine fibroids within the scope of the specific appropriate comparator therapy. However, ulipristal acetate is no longer eligible as part of the appropriate comparator therapy due to the repeal of the European marketing authorisation for the medicinal product Esmya on 18 July 2024.

For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy at the present time. 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 linzagolix is assessed as follows:

For adult women of reproductive age with moderate to severe symptoms of uterine fibroids, the additional benefit is not proven.

Justification:

For adult women of reproductive age with moderate to severe symptoms of uterine fibroids, no direct comparator studies versus the appropriate comparator therapy are available. In addition, as part of their systematic search, the pharmaceutical company could not identify any suitable studies for an indirect comparison of linzagolix with the appropriate comparator therapy.

However, the data from the randomised controlled approval studies PRIMROSE 1 and PRIMROSE 2, in which linzagolix was compared with placebo, were also presented in the dossier. During the entire study phase, the use of all treatment options listed in the G-BA's appropriate comparator therapy was prohibited. The studies are thus unsuitable for deriving an additional benefit of linzagolix compared to the appropriate comparator therapy.

In the overall assessment, an additional benefit of linzagolix over the appropriate comparator therapy is not proven for adult women of reproductive age with moderate to severe symptoms of uterine fibroids.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Yselty with the active ingredient linzagolix. Linzagolix is indicated for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The G-BA determined an individualised therapy with a choice of symptom-oriented treatment with relugolix/ estradiol/ norethisterone acetate or progestogens (for patients for whom symptomatic treatment of menorrhagia, hypermenorrhoea is sufficient) and invasive treatment options as the appropriate comparator therapy.

For adult women of reproductive age with moderate to severe symptoms of uterine fibroids, the pharmaceutical company could not identify any suitable studies for a direct or indirect comparison of linzagolix with the appropriate comparator therapy.

In the randomised controlled approval studies PRIMROSE 1 and PRIMROSE 2, in which linzagolix was compared with placebo, the use of all treatment options listed in the appropriate comparator therapy was prohibited during the entire study phase. Based on these studies, an additional benefit of linzagolix over the appropriate comparator therapy cannot therefore be derived.

In the overall assessment, an additional benefit of linzagolix over the appropriate comparator therapy is thus not proven for adult women of reproductive age with moderate to severe symptoms of uterine fibroids.

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).

This resolution is based on the information from the resolution of the benefit assessment procedure for the combination of active ingredients relugolix/ E2/ NETA of 17 February 2022. There are uncertainties both in the patient numbers submitted by the pharmaceutical company in this benefit assessment procedure and in those from the resolution on relugolix/ E2/ NETA. However, the calculation presented does not represent a better estimate compared to relugolix/ E2/ NETA due to the presence of further methodological uncertainties in the present procedure, the extent of which cannot be quantified. Therefore, the uncertainty is taken into account to a greater extent by the wider range in the previous procedure. The points of criticism regarding the estimate of the patient numbers described in the justification for the resolution of 17 February 2022 remain valid.

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 Yselty (active ingredient: linzagolix) at the following publicly accessible link (last access: 10 January 2025):

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

Treatment with linzagolix should only be initiated and monitored by doctors experienced in treating patients with uterine fibroids.

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 February 2025).

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

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 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 (Levosert, last revised July 2024).

According to the product information, linzagolix can be used together with an add-back therapy consisting of 1 mg estradiol (E2) and 0.5 mg norethisterone acetate (NETA). Women for whom add-back therapy is not recommended or who wish to avoid hormone therapy can

take 100 mg indefinitely. The intake of 200 mg without add-back therapy is limited to a period of 6 months. Therapy discontinuation after this period of 6 months is not considered to be a normal case and is therefore not included in the calculation of costs.

Costs of invasive treatment methods

Invasive treatment options include hysterectomy, myomectomy or (percutaneous transcatheter) embolisation. Percutaneous transcatheter embolisation can only be performed safely in an inpatient setting. The surgical procedures hysterectomy and myomectomy can be performed on an outpatient or inpatient basis, but these are predominantly performed on an inpatient basis. Cost representation is done by taking the example of the (approximate) costs incurred in the inpatient sector. It should be noted that different billing terms and fees would have to be taken into account in the outpatient sector.

The inpatient costs are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG (Diagnosis Related Group) multiplied by the federal base rate value of 2024 (€ 4,200). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee according to Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (since 1 January 2024: € 230) and the treatment-specific nursing revenue valuation ratio.

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				
Linzagolix	Continuously, 1 x daily	365.0	1.0	365.0
E2/ NETA	Continuously, 1 x daily	365.0	1.0	365.0
Appropriate comparator therapy				
Individualised therapy with a choice of: symptom-oriented treatment such as relugolix/ estradiol/ norethisterone acetate and progestogens as well as invasive treatment options				
Symptom-oriented treatment				
Relugolix/ E2/ NETA	Continuously, 1 x daily	365.0	1.0	365.0
Chlormadinone	on day 16 - 25 of a cycle	13.0	10.0	130.0
Levonorgestrel	1 x for up to 5 years	1.0	1.0	1.0
Invasive treatment options				
Hysterectomy	once		3.3 – 3.9 (average length of stay)	

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Myomectomy	once[2]		2.7 - 3.6 (average length of stay)	
Percutaneous transluminal angioplasty	once[2]		4.2 (average length of stay)	

Consumption:

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					
Linzagolix	100 mg 200 mg	100 mg – 200 mg	1 x 100 mg – 1 x 200 mg	365.0	365 x 100 mg – 365 x 200 mg[3]
E2/ NETA	1 mg/ 0.5 mg	1 mg/ 0.5 mg	1 x 1 mg/ 0.5 mg	365.0	365 x 1 mg/ 0.5 mg
Appropriate comparator therapy					
Symptom-oriented treatment					
Relugolix/ E2/ NETA	40 mg/ 1 mg/ 0.5 mg	40 mg/ 1 mg/ 0.5 mg	1 x 40 mg/ 1 mg/ 0.5 mg	365.0	365 x 40 mg/ 1 mg/ 0.5 mg
Chlormadinone	2 mg – 4 mg	2 mg – 4 mg	1 x 2 mg – 2 x 2 mg	130.0	130 x 2 mg – 260 x 2 mg
Levonorgestrel	20 µg	20 µg	20 µg	1.0	1 intrauterine pessary
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

[2]Treatment can be repeated if necessary.
[3]Administration of 200 mg linzagolix without add-back therapy (ABT) is limited to less than 6 months according to the product information.

in accordance with Sections 130 and 130 a 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 reference prices 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					
Linzagolix 100 mg	84 FCT	€ 323.86	€ 1.77	€ 17.30	€ 304.79
Linzagolix 200 mg	84 FCT	€ 323.86	€ 1.77	€ 17.30	€ 304.79
E2 1 mg/ NETA 0.5 mg[4]	84 FCT	€ 37.41	€ 1.77	€ 2.06	€ 33.58
Appropriate comparator therapy					
Relugolix 40 mg/ E2 1 mg/ NETA 0.5 mg	84 FCT	€ 279.01	€ 1.77	€ 14.82	€ 262.42
Chlormadinone 2 mg	100 TAB	€ 40.15	€ 1.77	€ 1.60	€ 36.78
Levonorgestrel 52 mg	1 IUP	€ 132.10	€ 1.77	€ 15.28	€ 115.05
Abbreviations: FCT = film-coated tablets, TAB = tablet, IUP = intrauterine pessary					

LAUER-TAXE® last revised: 15 February 2025

[4]Fixed reimbursement rate

Costs of invasive treatment methods

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value 2024	Nursing revenue valuation ratio	Nursing fee 2024	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Hysterectomy									
2024	N07A	3.3	0.861	€ 4,210.59	0.8194	€ 250	€ 3,625.32	€ 676.01	€ 4,301.33
2024	N21A	3.9	1.174	€ 4,210.59	0.8172	€ 250	€ 4,943.23	€ 796.77	€ 5,740.00
Myomectomy									
2024	N23Z	3.6	1.054	€ 4,210.59	0.8664	€ 250	€ 4,437.96	€ 779.76	€ 5,217.72
2024	N25Z	2.7	0.73	€ 4,210.59	0.908	€ 250	€ 3,073.73	€ 612.90	€ 3,686.63
Percutaneous transluminal angioplasty									
2024	N06Z	4.2	1.099	€ 4,210.59	0.8117	€ 250	€ 4,627.44	€ 852.29	€ 5,479.73

<u>Costs for additionally required SHI services:</u>

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 (Levosert, last revised July 2024), only the costs for insertion are taken into account as additional costs for the first year.

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 an intrauterine pessary due to a disease GOP 08330	€ 7.68	1	€ 7.68

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 requirements 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:

Adult women of reproductive age with moderate to severe symptoms of uterine fibroids:

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

References:
Product information for linzagolix (Yselty); Yselty 100 mg and 200 mg film-coated tablets; last revised: November 2024

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 25 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 6 September 2024, the pharmaceutical company submitted a dossier for the benefit assessment of linzagolix to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 10 September 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 linzagolix.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 16 December 2024. The deadline for submitting statements was 6 January 2025.

The oral hearing was held on 27 January 2025.

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 25 February 2025, and the proposed draft resolution was approved.

At its session on 6 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	1 November 2022	Determination of the appropriate comparator therapy
Working group Section 35a	14 January 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 January 2025	Conduct of the oral hearing
Working group Section 35a	5 February 2025 19 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 February 2025	Concluding discussion of the draft resolution
Plenum	6 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 March 2025

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

Prof. Hecken