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) Fezolinetant (vasomotor symptoms (VMS), associated with menopause)

of 1 August 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient fezolinetant on 1 February 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 25 January 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 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 fezolinetant 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 fezolinetant.

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 Fezolinetant (Veoza) in accordance with the product information

Veoza is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Therapeutic indication of the resolution (resolution of 1 August 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) <u>Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment</u>

Appropriate comparator therapy for fezolinetant:

- Therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/progestogen combination in women with an intact uterus or oestrogen only in women without a uterus)

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

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Appropriate comparator therapy for fezolinetant:

- Monitoring wait-and-see approach

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 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. For the systemic treatment of oestrogen deficiency symptoms in postmenopausal women with an intact uterus or in women without a uterus, oestrogens in combination with progestogens or only oestrogens are considered as approved medicinal products in the therapeutic indication.

on 2. Non-medicinal treatment that can be provided within the SHI framework is not an option in this therapeutic indication.

on 3. No resolutions are available.

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 indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”).

The evidence search identified guidelines, including an S3 guideline from the German Society of Gynaecology and Obstetrics, with recommendations for the treatment of postmenopausal symptoms in menopausal women. In summary, it has been shown that hormone replacement therapy with oestrogens (and possibly progestogens) is most effective in alleviating vasomotor symptoms. However, it should be noted that the placebo response rate is also relatively high and the guidelines recommend hormone replacement therapy (oestrogen/ progestogen combination in women with an intact uterus or only oestrogen in women without a uterus) not without a clear indication and after clarification of the individual risk-benefit profile, also due to possible and known side effects. Against this background, a distinction is made between two patient groups in this therapeutic indication.

In group a) menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment, the appropriate comparator therapy will be a therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/ progestogen combination in women with an intact uterus or only oestrogen in women without a uterus).

In group b) menopausal women with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or who have decided against therapy after individual risk-benefit assessment, the "monitoring wait-and-see approach" is determined to be the appropriate comparator therapy. It is assumed that the patients in groups a) and b) are postmenopausal.

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 fezolinetant is assessed as follows:

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

Extent and probability of the additional benefit of fezolinetant compared to the appropriate comparator therapy:

An additional benefit is not proven.

Justification:

No data are available for the assessment of the additional benefit of fezolinetant compared with the appropriate comparator therapy in menopausal patients with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment. An additional benefit is therefore not proven.

b) Menopausal women with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Extent and probability of the additional benefit of fezolinetant compared to a monitoring wait-and-see approach:

Hint for a minor additional benefit

Justification:

For the assessment of the additional benefit of fezolinetant compared with the appropriate comparator therapy in menopausal patients with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or have decided against therapy after individual risk-benefit assessment, the pharmaceutical company is presenting results from the DAYLIGHT study and results from sub-populations of the SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 studies.

DAYLIGHT

The DAYLIGHT study is a randomised, controlled, double-blind study in which a total of 453 patients were treated with fezolinetant or placebo in a 1:1 ratio. Menopausal women aged 40 to 65 years with moderate to severe vasomotor symptoms associated with menopause were enrolled. Patients had to have reported at least 7 moderate to severe hot flashes per day on an average in the last 10 days before randomisation. To fulfil the inclusion criterion "who are ineligible for hormone replacement therapy", at least 1 of the following four criteria had to be met: Presence of a contraindication (e.g. patients with a history of breast cancer or oestrogen-dependent tumours), a risk factor (e.g. patients with a history of diabetes mellitus), discontinuation of hormone replacement therapy (due to lack of efficacy, the occurrence of side effects or on medical advice) or decision against hormone replacement therapy.

The study comprises a screening phase of up to 3 weeks, a 24-week double-blind treatment phase and a 3-week follow-up phase for adverse events.

The study was conducted in several study sites in Europe and North America between November 2021 and April 2023.

SKYLIGHT 1 and SKYLIGHT 2:

The SKYLIGHT 1 and SKYLIGHT 2 studies were randomised, controlled, double-blind studies in which two doses of fezolinetant were compared with placebo. Menopausal women aged 40 to 65 years with moderate to severe vasomotor symptoms associated with menopause were enrolled. The studies comprised up to 50 days of screening and placebo-controlled treatment up to week 12. Treatment was then continued until week 52 as part of a uncontrolled extension phase. For the benefit assessment, the pharmaceutical company submitted results of a sub-population "who are ineligible for hormone replacement therapy", based on the 4 criteria contraindication (without porphyria), risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy.

SKYLIGHT 4

The SKYLIGHT 4 study is a randomised, controlled, double-blind study that enrolled menopausal women aged 40 to 65 years with vasomotor symptoms (associated with menopause), regardless of their severity. As the approved therapeutic indication for fezolinetant is limited to moderate to severe vasomotor symptoms and data on the frequency and/or severity of vasomotor symptoms are available neither for the total population nor for the sub-population of the SKYLIGHT 4 study presented in the dossier (patients who are

ineligible for hormone replacement therapy), the study is not considered for the present benefit assessment.

Consideration of the DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 studies

The operationalisation of the ineligibility for hormone replacement therapy is considered adequate for the criteria presence of a contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy. However, the risk factor criterion is not classified as an adequate criterion, as the listed risk factor diabetes mellitus, among others, is not a contraindication for hormone replacement therapy according to national and international scientific-medical societies.

For the DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 studies, the pharmaceutical company therefore subsequently submitted evaluations of a sub-population of each study in the written statement procedure, which exclusively comprises patients with at least 1 of the criteria contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy. Patients with a risk factor for hormone replacement therapy are only considered if 1 of the above criteria was also fulfilled. The evaluations submitted by the pharmaceutical company on the sub-population of the DAYLIGHT study are taken into account for the benefit assessment.

As part of the written statement procedure, the Deutsche Gesellschaft für Gynäkologische Endokrinologie und Fortpflanzungsmedizin e.V. (German Society for Gynaecological Endocrinology and Reproductive Medicine) and the Deutsche Menopause Gesellschaft e.V. (German Menopause Society) stated that studies over 12 – 24 weeks were sufficient for a benefit assessment, as menopausal conditions do not represent a chronic disease state. In contrast, the Drugs Commission of the German Medical Association (AkdÄ) has criticised the duration (12 – 24 weeks) of the studies; a period of at least one year is required to assess long-term efficacy.

The G-BA assumes that fezolinetant is taken for the duration of the vasomotor symptoms; according to the product information, there are no limitations with regard to the treatment duration. Studies show that frequent hot flashes (on more than 6 days in the last 2 weeks) and moderate to severe hot flashes occur[2] on average over a period of 7.4 years and last around 4.5 years from the last menstrual period[3,4]. Taking into account the duration of the existing symptomatology in the present indication, a comparative study duration of 12 weeks is considered too short for the assessment of the additional benefit compared with the

[2] German Society of Gynaecology and Obstetrics (DGGG), Austrian Society of Gynaecology and Obstetrics (OEGGG), Swiss Society of Gynaecology and Obstetrics (SGGG). Peri- and postmenopause - Diagnostics and interventions; S3 guideline, long version 1.1 [online]. AWMF registry number 015-062. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2020.

[3] Avis NE, Crawford SL, Greendale G et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015; 175(4): 531-539. https://doi.org/10.1001/jamainternmed.2014.8063.

[4] Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Ageing Study cohort. Menopause 2014; 21(9): 924-932. https://doi.org/10.1097/GME.0000000000000196.

appropriate comparator therapy. The data presented from the SKYLIGHT 1 and SKYLIGHT 2 studies were therefore not considered for the benefit assessment.

Extent and probability of the additional benefit

Mortality

In the DAYLIGHT study, overall mortality, operationalised as AEs leading to death, was collected. No deaths have occurred.

Morbidity

For the endpoints in the categories of morbidity and health-related quality of life, responder analyses on the improvement at week 24 and continuous evaluations on the change compared to the start of the study are available. As the therapeutic goal in this therapeutic indication is an improvement in symptomatology, the analyses of the percentage of patients with an improvement at week 24 are used.

Moderate and severe vasomotor symptoms
The pharmaceutical company presented results for the endpoints of frequency and severity of vasomotor symptoms, among others. In doing so, the frequency was operationalised as the average number of daily moderate to severe hot flashes in a period of 7 days (or 10 days for the baseline value). The severity was determined as the weekly average of the weighted average number of daily moderate to severe hot flashes. According to the inclusion criteria, all patients in the DAYLIGHT study experienced an average of at least 7 moderate to severe hot flashes per day. Moderate hot flashes were defined as "sensation of heat with sweating but ability to continue activity" and severe hot flashes as "sensation of heat with sweating leading to cessation of activity". Data on the number of vasomotor symptoms broken down by severity are not available.

For the present benefit assessment, the percentage of patients with a 100% reduction in moderate and severe vasomotor symptoms (at week 24) compared to baseline is used. This operationalisation takes into account both the number and severity of the hot flashes experienced, so that the severity of the vasomotor symptoms is not considered separately.

In the written statement procedure, the pharmaceutical company also submitted evaluations on the frequency and severity of vasomotor symptoms of any severity (mild/ moderate/ severe).

Mild vasomotor symptoms are not covered by the approved therapeutic indication. In the DAYLIGHT study, these were defined as "sensation of heat without sweating". Since it remains unclear how often the reduction in moderate and severe vasomotor symptoms by 100% is due to an elimination of vasomotor symptoms or a reduction to mild vasomotor symptoms, the additional evaluation can provide further information on the endpoint. The percentage of patients with a 100% reduction in all vasomotor symptoms compared to baseline is therefore presented additionally in the benefit assessment.

For the endpoint of moderate and severe vasomotor symptoms (100% reduction), there was a statistically significant difference to the advantage of fezolinetant.

Change in vasomotor symptoms (surveyed via patient-reported global disease activity [PGI-C VMS])
The PGI-C VMS consists of a single question asking patients to assess the change in hot flashes/ night sweats at week 24 on a 7-point scale (from "much better" to "much worse") since the start of treatment. In the dossier, responder analyses defined post hoc were presented, taking into account patients who assessed their symptomatology as "very much better" or "much better" compared to the start of treatment. However, when answering the selected question of the PGI-C VMS, it is not clear whether the response refers to one of the two symptoms queried or to both. In addition, the responder analysis presented for the reduction of vasomotor symptoms provides an appropriate operationalisation of the vasomotor symptoms.
The endpoint of patient-reported global disease activity (PGI-C VMS) is therefore not used for the benefit assessment.

Sleep disorders (PROMIS SD SF 8b)
In the DAYLIGHT study, the short form of the PROMIS SD SF 8b questionnaire was used for the patient-reported survey of sleep disorders. PROMIS is a valid, generic system consisting of domain-specific instruments for self- and peer-reported assessment of physical, mental and social health. Contrary to the procedure described in the PROMIS manual, the evaluations in the dossier were not based on transformed values and were therefore unsuitable for the benefit assessment.
For the endpoint, the pharmaceutical company submitted post hoc responder analyses based on transformed values in the written statement procedure. According to the PROMIS manuals, there are 2 methods for transforming the raw values, whereby the method using the "response scoring pattern" should be preferred due to more accurate measurement and better handling of missing values. The pharmaceutical company does not state which transformation method was used.
For the present benefit assessment, the responder analysis conducted post hoc with an improvement of the PROMIS SD SF 8b by ≥ 7.14 points is used, as this response criterion corresponds to exactly 15% of the scale range (based on transformed values).
For the endpoint of sleep disorders (PROMIS SD SF 8b, improvement by ≥ 7.14 points), there was a statistically significant difference to the advantage of fezolinetant.

Patient Global Impression of Severity or Change of Sleep Disturbance (PGI-S SD and PGI-C SD)
In the DAYLIGHT study, sleep disorders were surveyed using the PGI-S SD and PGI-C SD in addition to the PROMIS. Each of these consists of a single question on the severity or change in sleep disorders. However, the PROMIS SD SF 8b is a valid instrument for surveying sleep disorders, covering sleep disorders in detail across several questions. The PGI-S SD and the PGI-C SD are therefore not used for the benefit assessment.

Female sexual function (FSFI)
The FSFI consists of 19 questions on various aspects of sexuality, which are summarised in 6 domains (desire, arousal, lubrication, orgasm, general satisfaction and pain) and relates to the last 4 weeks. The individual questions are answered on Likert scales from 1 to 5 or 0 to 5, with 0 indicating a lack of sexual activity in the last month. The scale range of the weighted total score is 2 to 36 points. For the present benefit assessment, responder analyses defined post hoc with an improvement in the FSFI total score by ≥ 5.1 points are used, as this response criterion corresponds to 15% of the scale range.

For the endpoint of female sexual function (FSFI, improvement by ≥ 5.1 points), there was no statistically significant difference between the treatment arms, either in the total score or in the individual domains.

General symptoms of depression and anxiety disorders (PHQ-4)
The PHQ-4 consists of 2 questions on depression and 2 questions on anxiety disorders and surveys the conditions in the last 2 weeks on a 4-point Likert scale. This results in a total score (scale range 0 to 12 points) and the two subscales of anxiety and depression (0 to 6 points each). For the present benefit assessment, responder analyses defined post hoc with an improvement in the PHQ-4 total score by ≥ 1.8 points are used, as this response criterion corresponds to 15% of the scale range.

For the endpoint of general symptoms of depression and anxiety disorders (PHQ-4, improvement by ≥ 1.8 points), there was no statistically significant difference between the treatment arms in either the total score or the two subscales.

Activity impairment (surveyed using Work Productivity and Activity Impairment [WPAI] question 6)
In the DAYLIGHT study, the WPAI questionnaire hot flashes/ night sweats was used. Question 6 measures the impairment of daily activities in the last 7 days on a scale from 0 to 10. Since activity impairment is already reflected by the daily indication of the severity of vasomotor symptoms in the electronic diary (severe hot flashes mean cessation of activity), the evaluations on activity impairment are not used for the benefit assessment.

Health status (EQ-5D VAS)
In the DAYLIGHT study, the health status was surveyed using the visual analogue scale (VAS) of the EQ-5D, which collects the patients' self-assessed health status on a scale from 0 (worst perceivable health status) to 100 (best perceivable health status).

For the endpoint of health status (EQ-5D VAS, improvement by ≥ 15 points), there was no statistically significant difference between the treatment arms.

Quality of life

Health-related quality of life (Menopause-Specific Quality of Life, MENQOL)
The version of the MENQOL questionnaire used in the DAYLIGHT study comprises a total of 29 items distributed across the 4 domains vasomotor, physical, psychosocial and sexual. The

questionnaire completed by the patients themselves assesses whether problems have occurred within the last 7 days and, if so, their severity.
For the evaluation, the result of each item is converted into a scale from 1 to 8 and the domain scores are calculated separately as the mean value of the corresponding items. The range of values is therefore also 1 to 8. Higher scores indicate more severe conditions. For the present benefit assessment, responder analyses defined post hoc with an improvement of the 4 domain scores by ≥ 1.05 points each are used, as this response criterion corresponds to 15% of the scale range of the subscales.

For the endpoint of health-related quality of life, surveyed using MENQOL, there was a statistically significant difference to the advantage of fezolinetant for all 4 domains (vasomotor, psychosocial, physical and sexual; improvement by ≥ 1.05 points in each case).

Side effects

The percentage of patients with study discontinuation was higher in the control arm (17%) than in the intervention arm (8%).

There was no statistically significant difference between the treatment groups for the endpoints of SAEs and discontinuation due to AEs.

Specific adverse events
For the endpoint of neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC, SAEs), no events occurred during the course of the study.
There was no statistically significant difference between the treatment arms for the endpoint of liver-related examinations, clinical signs and symptoms (SMQ, SAEs).

Overall assessment

For the assessment of the additional benefit of fezolinetant for menopausal women with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or have decided against therapy after individual risk-benefit assessment, evaluations of the double-blind, randomised, placebo-controlled phase III DAYLIGHT study are available at week 24. To derive an additional benefit, the sub-population which exclusively comprises patients who met at least 1 of the criteria contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy is considered.

No events occurred in the mortality endpoint category.

In the morbidity category, there was a statistically significant advantage in favour of fezolinetant over the appropriate comparator therapy at study week 24 for the endpoint of reduction in moderate and severe vasomotor symptoms by 100% and for the endpoint of sleep disorders (surveyed using PROMIS SD SF 8b). There were no statistically significant differences between the treatment arms for the endpoints of sexual function (surveyed using the FSFI), general symptoms of depression and anxiety disorders (surveyed using the PHQ-4) and health status (surveyed using the EQ-5D VAS).

In the health-related quality of life category (surveyed using MENQOL), a statistically significant advantage in favour of fezolinetant over the appropriate comparator therapy was observed at study week 24.

There were no statistically significant differences between the treatment arms in the side effects category.

Overall, there were statistically significant advantages of fezolinetant over the appropriate comparator therapy at week 24 in the endpoint category of morbidity and health-related quality of life.

However, there are relevant uncertainties when assessing the extent of impairment of the patients by the present vasomotor symptoms. No information is available on the number of vasomotor symptoms broken down by severity. Furthermore, the distinction between moderate and severe vasomotor symptoms is based solely on whether or not the activity being performed could be continued. Uncertainties also exist for the endpoint of sleep disorders, as it remains unclear whether the preferred transformation method was used for the evaluation. Fundamental uncertainties also arise from differences in the patient characteristics of the DAYLIGHT study: The average time since the onset of amenorrhoea was 72.9 months for patients in the intervention arm, compared with 56.9 months in the control arm. The time since the onset of hot flashes was comparable between the treatment arms (64.2 and 60.7 months respectively), but the menopausal conditions last longer if the first hot flashes occur before the menopause than if the conditions only begin after the menopause[2]. It is therefore unclear to what extent more patients in the intervention arm may have been in the study at a time when menopausal conditions were already decreasing.

For menopausal women with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or have decided against therapy after individual risk-benefit assessment, a minor additional benefit of fezolinetant compared with the appropriate comparator therapy of monitoring wait-and-see approach is therefore determined in the overall assessment, taking into account the uncertainties mentioned.

Reliability of data (probability of additional benefit)

The risk of bias across endpoints for the DAYLIGHT study is rated as low. However, the risk of bias for the results at endpoint level is rated as high. For the endpoints of morbidity and health-related quality of life, this is justified by the high percentages of substituted values (non-responder imputation) varying between the treatment arms. The different percentages of study discontinuations between the study arms represent an uncertainty for the endpoints on side effects.

The reliability of data is therefore rated as a hint.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Veoza with the active ingredient fezolinetant. The active ingredient is approved for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

A distinction was made between two patient populations in the therapeutic indication to be considered.

Patient population a) comprises menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment. The appropriate comparator therapy was determined to be a therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/ progestogen combination in women with an intact uterus or only oestrogen in women without a uterus).

No comparator data are available for this patient population compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

Patient population b) comprises menopausal women with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or have decided against therapy after individual risk-benefit assessment. The monitoring wait-and-see approach was determined as the appropriate comparator therapy. For this patient population, the pharmaceutical company presented results from the DAYLIGHT study and results from sub-populations of the SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 studies.

To derive an additional benefit, the results for the sub-population of the randomised, placebo-controlled, phase III DAYLIGHT study at week 24 are considered, which only includes patients who met at least 1 of the criteria contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy.

No events occurred in the mortality endpoint category.

In the morbidity category, there was a statistically significant advantage in favour of fezolinetant over the appropriate comparator therapy at study week 24 for the endpoint of reduction in moderate and severe vasomotor symptoms by 100% and for the endpoint of sleep disorders (surveyed using PROMIS SD SF 8b). There were no significant differences between the treatment arms for the endpoints of sexual function (surveyed using the FSFI), general symptoms of depression and anxiety disorders (surveyed using the PHQ-4) and health status (surveyed using the EQ-5D VAS).

In the health-related quality of life category (surveyed using MENQOL), a statistically significant advantage in favour of fezolinetant over the appropriate comparator therapy was observed at study week 24.

There were no statistically significant differences between the treatment arms in the side effects category.

Due to the lack of information on the number of vasomotor symptoms by severity and the defined distinction between moderate and severe vasomotor symptoms based solely on the continuation or cessation of an activity performed, the assessment of the extent of the patients' impairment results in relevant uncertainties. For the endpoint of sleep disorders, there are also uncertainties regarding the evaluation. There are further uncertainties with regard to patient characteristics, as it is unclear to what extent more patients in the intervention arm may have been in the study at a time when menopausal conditions were

already decreasing due to the varying length of time since the onset of amenorrhoea. The extent of the additional benefit is therefore rated as minor in the overall assessment.

Due to the high risk of bias in the results for all endpoints (among other things, due to discrepant percentages of substituted values), the reliability of data is classified as high, so that a hint is derived.

For menopausal women with moderate to severe vasomotor symptoms who are ineligible for hormone therapy or have decided against therapy after individual risk-benefit assessment, a hint for a minor additional benefit is therefore identified.

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 G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties and potentially underestimated with regard to the lower limit. When determining the number of postmenopausal women with moderate to severe vasomotor symptoms, there are uncertainties regarding the two publications used by the pharmaceutical company, as certain patients were partially excluded or it remains unclear whether the patients are already postmenopausal or how the moderate to severe vasomotor symptoms were operationalised.

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 Veoza (active ingredient: fezolinetant) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 16 April 2024):

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

The benefit of long-term treatment must be reviewed regularly since the duration of VMS can vary from one subject to another. Women undergoing oncological treatment (e.g. chemotherapy, radiotherapy, anti-hormone therapy) for breast cancer or other oestrogen-related malignancies were not enrolled in the clinical studies. Therefore, fezolinetant is not recommended for use in this population as safety and efficacy are unknown.

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: 15 July 2024).

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.

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Fezolinetant	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/progestogen combination in women with an intact uterus or oestrogen only in women without a uterus)				
Oestrogen/progestogen combination				
Estradiol + drospirenone	Continuously, 1 x daily	365.0	1	365.0
Oestrogen only				
Estradiol	Continuously, 1 x daily	365.0	1	365.0

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Fezolinetant	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

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					
Fezolinetant	45 mg	45 mg	1 x 45 mg	365.0	365.0 x 45 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions with a choice of systemic hormone replacement therapy (oestrogen/progestogen combination in women with an intact uterus or oestrogen only in women without a uterus)					
Oestrogen/progestogen combination					
Estradiol + drospirenone	1 mg/2 mg	1 mg/2 mg	1 x 1 mg/ 2 mg	365.0	365.0 x 1 mg/2 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
Oestrogen only					
Estradiol	1 mg – 2 mg	1 mg – 2 mg	1 x 1 mg - 1 x 2 mg	365.0	365.0 x 1 mg – 365.0 x 2 mg

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Fezolinetant	45 mg	45 mg	1 x 45 mg	365.0	365.0 x 45 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

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:

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

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					
Fezolinetant 45 mg	100 FCT	€ 264.18	€ 2.00	€ 14.00	€ 248.18
Appropriate comparator therapy					
Estradiol 1 mg/2 mg[5]	84 FCT	€ 37.41	€ 2.00	€ 2.06	€ 33.35
Estradiol 1 mg[5]	84 FCT	€ 18.55	€ 2.00	€ 0.57	€ 15.98
Estradiol 2 mg[5]	100 TAB	€ 22.90	€ 2.00	€ 0.92	€ 19.98
Abbreviations: FCT = film-coated tablets; TAB = tablet					

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b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

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					
Fezolinetant 45 mg	100 FCT	€ 264.18	€ 2.00	€ 14.00	€ 248.18
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: FCT = film-coated tablets					

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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.

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

[5] Fixed reimbursement rate

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:

a) Menopausal women with moderate to severe vasomotor symptoms who are eligible for hormone therapy and have decided in favour of hormone replacement therapy after individual risk-benefit assessment

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 fezolinetant (Veoza); Veoza™ 45 mg film-coated tablets; last revised: February 2024

b) Menopausal women with moderate to severe vasomotor symptoms who are not eligible for hormone therapy or have decided against therapy after individual risk-benefit assessment

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.

References:
Product information for fezolinetant (Veoza); Veoza™ 45 mg film-coated tablets; last revised: February 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 23 June 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 25 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of fezolinetant 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 January 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 fezolinetant.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 April 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2024. The deadline for submitting statements was 23 May 2024.

The oral hearing was held on 10 June 2024.

By letter dated 11 June 2024, 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 12 July 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 23 July 2024, and the proposed draft resolution was approved.

At its session on 1 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 June 2020	Determination of the appropriate comparator therapy
Working group Section 35a	4 June 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 June 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 June 2024 17 July 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 July 2024	Concluding discussion of the draft resolution
Plenum	1 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 August 2024

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

Prof. Hecken