Fezolinetant (menopausal women with vasomotor symptoms)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
BRCA	breast cancer susceptibility gene
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PROMIS	Patient-Reported Outcomes Measurement Information System
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug fezolinetant. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 January 2024.

Research question

The aim of this report is to assess the added benefit of fezolinetant in comparison with the appropriate comparator therapy (ACT) in patients with moderate to severe vasomotor symptoms associated with the menopause.

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

Table 2: Research questions of the benefit assessment of fezolinetant

Research question	Therapeutic indication	ACT[a]
1	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is an option and who have decided in favour of hormone replacement therapy after an individual risk-benefit assessment[b]	Treatment of physician's choice choosing from systemic hormone replacement therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])[c]
2	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is not an option, or those who have decided against therapy after individual risk-benefit assessment[b]	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the patients in research questions 1 and 2 are postmenopausal.
c. For the implementation of the ACT for research question 1, a single comparator study is generally not sufficient. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

In the present assessment, the following designations are used for the patient populations of the 2 research questions:

- Research question 1: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is an option

- Research question 2: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option

The company followed the specification of the ACT for both research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving the added benefit.

Research question 1: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is an option

Results

Concurring with the company, no relevant study was identified for research question 1.

Results on added benefit

No data are available for the assessment of the added benefit of fezolinetant in comparison with the ACT in patients with moderate to severe vasomotor symptoms who are candidates for hormone replacement therapy. There is no hint of an added benefit of fezolinetant in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option.

Results

The check of the information retrieval identified the studies DAYLIGHT and SKYLIGHT 4 on the direct comparison of fezolinetant versus watchful waiting, for which it can be assumed (based on the available information) that they contain a subpopulation relevant for research question 2 of the present benefit assessment. For the data on these studies presented by the company, however, it is not sufficiently certain that at least 80 % of the patients correspond to research question 2. The data are therefore unsuitable for drawing conclusions on the added benefit for the relevant population for research question 2 of the present benefit assessment. In the following, the studies are first described and then the lack of suitability of the data presented for the benefit assessment is justified. Furthermore, reasons are given why the other studies used by the company (SKYLIGHT 1 and SKYLIGHT 2) are not suitable for the benefit assessment.

Evidence provided by the company

The company identified the four studies DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 for the direct comparison of fezolinetant versus watchful waiting. While the DAYLIGHT study only included patients for whom the company considered hormone replacement therapy to

be unsuitable, the company presented corresponding subpopulations for the studies SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 in its dossier.

For the benefit assessment, the company used meta-analyses of the RCTs DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 at Week 12 (fezolinetant: N = 1039 vs. placebo: N = 1038) and additionally presented meta-analyses of the RCTs DAYLIGHT and SKYLIGHT 4 at Week 24 (fezolinetant: N = 752 vs. placebo: N = 741) as well as the results of the individual studies at Week 12 and, if available, at Weeks 24 and 52.

DAYLIGHT study

The DAYLIGHT study is a double-blind RCT comparing fezolinetant with placebo.

Menopausal women aged 40 to 65 years with moderate to severe vasomotor symptoms associated with menopause were included. Patients had to have reported an average of at least 7 moderate to severe hot flushes per day in the last 10 days before randomization. According to the inclusion criteria, patients also had to be no candidates for hormone replacement therapy. At least 1 of the following criteria had to be fulfilled:

- Contraindication: patients with unexplained vaginal bleeding, a history of breast cancer or oestrogen-dependent tumours, arterial thromboembolic diseases or hypersensitivity to oestrogen and progesterone therapy or porphyria
- Risk factor: patients with a history of diabetes mellitus, hyperlipidaemia, migraine, obesity (body mass index [BMI] > 29.9 kg/m^2), systemic lupus erythematosus, epilepsy, family history of breast cancer in first-degree relatives or breast cancer susceptibility gene (BRCA)-1 and BRCA2 mutation or smoking status (current)
- Discontinuation of hormone replacement therapy: patients who have discontinued hormone replacement therapy due to lack of efficacy, the occurrence of side effects or on medical advice (duration of hormone replacement therapy or age of the patient [≥ 60 years])
- Decision against hormone replacement therapy: patients who refused hormone replacement therapy after a medical consultation

A total of 453 patients were randomly assigned in a 1:1 ratio to either 24-week treatment with fezolinetant (N = 227) or placebo (N = 226).

Administration of fezolinetant in the study was largely in compliance with the recommendations of the Summary of Product Characteristics (SPC). In the comparator arm, the patients received placebo. Since regular visits (every 2 to 4 weeks) took place in the study and the S3 guideline on perimenopause and postmenopause does not specify any

recommendations for action or specific parameters to be observed, this is considered to be a sufficient approximation to the ACT “watchful waiting” in this therapeutic indication.

Primary outcome of the study was the mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 24. According to the information in Module 4 A, patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

SKILIGHT 4 study

In the double-blind RCT SKYLIGHT 4, fezolinetant was compared with placebo over a 52-week treatment period.

Women aged 40 to 65 years with menopause-associated vasomotor symptoms were included. According to the inclusion criteria, there was no restriction to patients with moderate to severe vasomotor symptoms.

Participation in the study was not restricted to patients who were not eligible for hormone replacement therapy. The company therefore formed a subpopulation post hoc for the benefit assessment based on the 4 criteria of contraindication (without porphyria), risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy. The subpopulation of the SKYLIGHT 4 study analysed by the company comprised 526 patients in the fezolinetant arm and 515 patients in the placebo arm.

Administration of fezolinetant in the study was largely in compliance with the recommendations of the SPC. In the comparator arm, the patients received placebo. Since regular visits (every 2 to 4 weeks) took place in the study, this is considered to be a sufficient approximation to the ACT watchful waiting in the present therapeutic indication.

The primary outcomes of the study were the frequency and severity of adverse events (AEs) and the proportion of patients with endometrial hyperplasia or carcinoma. According to the information in Module 4 A, patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Studies 1 SKYLIGHT and 2

The studies SKYLIGHT 1 and SKILIGHT 2 are double-blind RCTs comparing fezolinetant with placebo. Both studies were planned and conducted nearly analogously. The inclusion and exclusion criteria for both studies were identical.

Women aged 40 to 65 years with moderate to severe menopause-associated vasomotor symptoms were included. According to the inclusion criteria, these patients had to have

experienced an average of at least 7 to 8 moderate to severe hot flushes per day or 50 to 60 moderate to severe hot flushes per week in the last 10 days before randomization.

Participation in the study was not restricted to patients who were not eligible for hormone replacement therapy. The company therefore formed a subpopulation for the benefit assessment based on the 4 criteria of contraindication (without porphyria), risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy. The subpopulation of the SKYLIGHT 1 study analysed by the company comprised 142 patients in the fezolinetant arm and 148 patients in the placebo arm. For the SKYLIGHT 2 study, there were 145 patients in the fezolinetant arm and 149 patients in the placebo arm.

Both studies comprise a double-blind placebo-controlled phase up to Week 12 and a subsequent non-controlled extension phase. In the 40-week extension phase, patients in the placebo arm were randomly assigned to treatment with fezolinetant (30 mg/day or 45 mg/day). Patients who were assigned to one of the two fezolinetant arms at the start of the study continued their treatment in the extension phase.

Administration of fezolinetant was largely in compliance with the recommendations of the SPC in both studies. In the comparator arm, the patients received placebo. Since regular visits (every 2 to 4 weeks) took place in the study, this is considered to be a sufficient approximation to the ACT watchful waiting in the present therapeutic indication.

The co-primary outcomes in both studies were defined as the frequency and severity of moderate to severe vasomotor symptoms at Week 4 and Week 12. According to the information in Module 4 A, patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Suitability of the evidence presented by the company for research question 2

Operationalization of “hormone replacement therapy is not an option” not adequate

The company used the 4 criteria of contraindication, risk factor, discontinuation of hormone replacement therapy and the decision against hormone replacement therapy after a medical consultation to characterize the patient group covered by research question 2. Patients were assigned to research question 2 if at least 1 criterion was fulfilled.

Research question 2 explicitly includes patients who decided against hormone replacement therapy following a risk-benefit assessment - regardless of whether the treatment was suitable for the patient or not. The criterion "decision against hormone replacement therapy after a medical consultation" defined by the company is therefore considered adequate. The same applies to the criterion “discontinuation of hormone replacement therapy”. In these patients, it can be assumed that a consultation took place before the start of hormone replacement therapy and that the discontinuation of therapy also took place in consultation

with the attending physician. The criterion “contraindication” defined by the company is in line with the recommendations of national and international scientific societies and is therefore also adequate.

The situation is different for the criterion “risk factor”. According to national and international scientific societies, the risk factor of diabetes mellitus listed by the company does not represent a contraindication for hormone replacement therapy; rather, hormone replacement therapy can also be considered for these patients after an individual risk-benefit assessment. The risk factor “hyperlipidaemia” also does not appear to be suitable for ruling out the eligibility of hormone replacement therapy in principle. There is little or no evidence for the other risk factors mentioned by the company, so that a patient-specific decision should also be made here. Accordingly, without further risk-benefit assessment, the risk factor “criterion” is not suitable for defining the patient population for whom hormone replacement therapy is not an option.

In the DAYLIGHT study, the largest proportion of patients were included in the study based on the criteria “decision against hormone replacement therapy after a medical consultation” (37.2%) and “presence of a risk factor” (36.5%). 15.3% of patients belonged to the treatment group “discontinuation of hormone replacement therapy” and 11.1% had a contraindication. Due to the high proportion of patients with the criterion “risk factor” in combination with the lack of information on how many of these patients also fulfilled a second criterion, it is not sufficiently ensured for the reasons explained above that at least 80% of the patients in the DAYLIGHT study were to be assigned to research question 2.

In the 3 SKYLIGHT studies, ineligibility for hormone replacement therapy was not an inclusion criterion for participation in the study. For the subpopulations of these studies presented by the company, no information is available on the distribution of patients to the various criteria. For the 3 SKYLIGHT studies, it is therefore unclear whether at least 80% of the patients in the subpopulations corresponded to research question 2.

SKYLIGHT 4: No restriction to moderate to severe vasomotor symptoms

Patients with vasomotor symptoms could be included in the SKYLIGHT 4 study regardless of their severity. Data on the frequency and/or severity of the vasomotor symptoms are neither available for the total population nor for the subpopulation of the SKYLIGHT 4 study presented in the dossier. Besides the uncertainty regarding the ineligibility for hormone replacement therapy, it is thus unclear for the subpopulation of the SKYLIGHT 4 study used by the company for the benefit assessment whether moderate to severe vasomotor symptoms were present in at least 80% of the patients-according to the approval of fezolinetant.

SKYLIGHT 1 and SKYLIGHT 2: study duration too short

According to the SPC, there is no restriction on the treatment duration for fezolinetant. It is therefore assumed that fezolinetant is administered for the duration of the vasomotor symptoms.

In the patient population from the studies DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 presented by the company, hot flushes had been occurring for an average of 75 days. Studies show that frequent hot flushes (on more than 6 days in the last 2 weeks) and moderate to severe hot flushes last for about 4.5 years. The duration of the symptoms therefore also supports the minimum study duration of 24 weeks chosen in this assessment.

In the studies SKYLIGHT 1 and SKYLIGHT 2, the placebo-controlled phase lasted only 12 weeks in each case. Therefore, the data presented for these two studies are not suitable for the benefit assessment.

Summary

The company defined the ineligibility for hormone replacement therapy on the basis of the criteria of contraindication, risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy, of which at least 1 criterion had to be fulfilled. As described above, hormone replacement therapy can generally also be considered in the presence of a risk factor. Therefore, this criterion is not adequate to determine an assignment to research question 2 of the benefit assessment.

For the DAYLIGHT study presented by the company and for the subpopulations of the studies SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 presented, it is therefore not sufficiently ensured that at least 80% of the patients correspond to research question 2. In addition, the studies SKYLIGHT 1 and SKYLIGHT 2 with a comparative treatment period of 12 weeks are too short, and for the SKYLIGHT 4 study it is unclear how many patients in the subpopulation had moderate to severe vasomotor symptoms.

In summary, based on the information available, it can still be assumed that the studies DAYLIGHT and SKYLIGHT 4 each contain a relevant subpopulation for research question 2 of the present benefit assessment. However, as described, the data of the two studies presented by the company are not suitable for deriving conclusions on the added benefit of fezolinetant in comparison with the ACT for research question 2 of the present benefit assessment. As part of the commenting procedure, the company has to present analyses for the relevant subpopulation that comprises patients with moderate to severe menopause-associated vasomotor symptoms who fulfil one of the criteria defined by the company: contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy.

Results on added benefit

No suitable data are available for the assessment of the added benefit of fezolinetant in comparison with the ACT in patients with moderate to severe vasomotor symptoms who are no candidates for hormone replacement therapy. There is no hint of an added benefit of fezolinetant in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 summarizes the result of the assessment of the added benefit of fezolinetant in comparison with the ACT.

Table 3: Fezolinetant – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is an option and who have decided in favour of hormone replacement therapy after an individual risk-benefit assessment[b]	Treatment of physician's choice choosing from systemic hormone replacement therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])c	Added benefit not proven
2	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is not an option, or those who have decided against therapy after individual risk-benefit assessment[b]	Watchful waiting	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the patients in research questions 1 and 2 are postmenopausal.
c. For the implementation of the ACT for research question 1, a single comparator study is generally not sufficient. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of fezolinetant in comparison with ACT in patients with moderate to severe vasomotor symptoms associated with the menopause.

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

Table 4: Research questions of the benefit assessment of fezolinetant

Research question	Therapeutic indication	ACT[a]
1	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is an option and who have decided in favour of hormone replacement therapy after an individual risk-benefit assessment[b]	Treatment of physician's choice choosing from systemic hormone replacement therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])c
2	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is not an option, or those who have decided against therapy after individual risk-benefit assessment[b]	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the patients in research questions 1 and 2 are postmenopausal.
c. For the implementation of the ACT for research question 1, a single comparator study is generally not sufficient. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

In the present assessment, the following designations are used for the patient populations of the 2 research questions:

- Research question 1: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is an option
- Research question 2: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option.

The company followed the specification of the ACT for both research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit (see also Section I 4.1). This departs from the inclusion criteria used by the company, which applied no restrictions regarding the minimum duration.

I 3 Research question 1: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is an option

I 3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on fezolinetant (status: 18 December 2023)
- bibliographical literature search on fezolinetant (last search on 01 December 2023)
- search in trial registries/trial results databases for studies on fezolinetant (last search on 18 December 2023)
- search on the G-BA website for fezolinetant (last search on 18 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on fezolinetant (last search on 13 February 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study.

I 3.2 Results on added benefit

No data are available for the assessment of the added benefit of fezolinetant in comparison with the ACT in patients with moderate to severe vasomotor symptoms who are candidates for hormone replacement therapy. There is no hint of an added benefit of fezolinetant in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of fezolinetant in comparison with the ACT in menopausal patients with moderate to severe vasomotor symptoms who are candidates for hormone replacement therapy, the added benefit is not proven.

I 4 Research question 2: menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option

I 4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on fezolinetant (status: 18 December 2023)
- bibliographical literature search on fezolinetant (last search on 01 December 2023)
- search in trial registries/trial results databases for studies on fezolinetant (last search on 18 December 2023)
- search on the G-BA website for fezolinetant (last search on 18 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on fezolinetant (last search on 13 February 2024); for search strategies, see I Appendix A of the full dossier assessment

The check identified the studies DAYLIGHT [3,4] and SKYLIGHT 4 [5-7] for the direct comparison of fezolinetant versus watchful waiting, for which (based on the available information) it can be assumed that they comprise a relevant subpopulation for research question 2 of the present benefit assessment.

In addition to the studies DAYLIGHT and SKYLIGHT 4, the company also identified the studies SKYLIGHT 1 [8-10] and SKYLIGHT 2 [11-13] and used meta-analyses of the RCTs DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 at Week 12 for the benefit assessment (fezolinetant: N = 1039 vs. Placebo: N = 1038). In addition, the company presented meta-analyses of the RCTs DAYLIGHT and SKYLIGHT 4 at Week 24 (fezolinetant: N = 752 vs. placebo: N = 741) as well as the results of the individual studies at Week 12 and, if available, at Weeks 24 and 52.

While the DAYLIGHT study only included patients for whom the company considered hormone replacement therapy to be unsuitable, the company presented corresponding subpopulations for the studies SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 in its dossier. However, the company defined the patient population for whom hormone replacement therapy is not an option on the basis of various criteria, not all of which are suitable.

Even if it can be assumed that the studies DAYLIGHT and SKYLIGHT 4 each comprised a relevant subpopulation for research question 2, it is not sufficiently certain for the data presented by the company on the two studies that at least 80% of the patients corresponded to research question 2. The data are therefore not suitable for drawing conclusions on the

added benefit for the patient population covered by research question 2. In the following, the studies are first described and then the lack of suitability of the data presented for the benefit assessment is justified. Furthermore, it is explained why the other studies used by the company (SKYLIGHT 1 and SKYLIGHT 2) are not suitable for the benefit assessment.

Evidence provided by the company

For a characterization of the studies described below, see also Table 6 and Table 7 in I Appendix B of the full dossier assessment.

DAYLIGHT study

The DAYLIGHT study is a double-blind RCT comparing fezolinetant with placebo.

Menopausal women aged 40 to 65 years with moderate to severe vasomotor symptoms associated with menopause were included. Patients had to have reported an average of at least 7 moderate to severe hot flushes per day in the last 10 days before randomization. According to the inclusion criteria, patients also had to be no candidates for hormone replacement therapy. At least 1 of the following criteria had to be fulfilled:

- Contraindication: patients with unexplained vaginal bleeding, a history of breast cancer or oestrogen-dependent tumours, arterial thromboembolic diseases or hypersensitivity to oestrogen and progesterone therapy or porphyria
- Risk factor: patients with a history of diabetes mellitus, hyperlipidaemia, migraine, obesity (BMI > 29.9 kg/m^2), systemic lupus erythematosus, epilepsy, family history of breast cancer in first-degree relatives or BRCA 1 and BRCA 2 mutation or smoking status (current)
- Discontinuation of hormone replacement therapy: patients who have discontinued hormone replacement therapy due to lack of efficacy, the occurrence of side effects or on medical advice (duration of hormone replacement therapy or age of the patient [≥ 60 years])
- Decision against hormone replacement therapy: patients who refused hormone replacement therapy after a medical consultation

A total of 453 patients were randomly assigned in a 1:1 ratio to either treatment with fezolinetant (N = 227) or placebo (N = 226). Stratification was based on smoking status (smoker vs. non-smoker).

The study comprised a screening phase of up to 3 weeks, a 24-week double-blind treatment phase and a 3-week follow-up phase for (AEs).

Administration of fezolinetant in the study was largely in compliance with the recommendations of the SPC [14]. Instead of the approved 45 mg film-coated tablet, 2 film-coated tablets of 30 mg and 15 mg were used. Bioequivalence of the two formulations was proven as part of the approval on the basis of study 2693-CL-0010 [15,16]. In the comparator arm, patients received placebo. The study was thus not designed for a comparison with watchful waiting. Since regular visits (every 2 to 4 weeks) took place in the study and the S3 guideline on perimenopause and postmenopause does not specify any recommendations for action or specific parameters to be observed [17], this is overall considered to be a sufficient approximation to the ACT "watchful waiting" in this therapeutic indication.

Primary outcome of the study was the mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 24. According to the information in Module 4 A, patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

SKILIGHT 4 study

The double-blind RCT SKYLIGHT 4 compared fezolinetant with placebo.

Women aged 40 to 65 years with menopause-associated vasomotor symptoms were included. According to the inclusion criteria, there was no restriction to patients with moderate to severe vasomotor symptoms. The BMI had to be between 18 and 38 kg/(m^2 .

The study enrolled a total of 1831 patients, who were randomized in a 1:1:1 ratio either to treatment with fezolinetant 30 mg/day, fezolinetant 45 mg/day or placebo. Stratification was based on smoking status (smoker vs. non-smoker). Since a fezolinetant dose of 30 mg is not covered by the approval [14], this study arm is not considered further by the company in the dossier. This approach is appropriate.

Participation in the study was not restricted to patients who were not eligible for hormone replacement therapy. The company therefore formed a subpopulation post hoc for the benefit assessment based on the 4 criteria of contraindication (without porphyria), risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy (see section on the DAYLIGHT study). The subpopulation of the SKYLIGHT 4 study analysed by the company comprised 526 patients in the fezolinetant arm and 515 patients in the placebo arm.

The study consists of a screening phase of up to 50 weeks, followed by a 52-week treatment phase and a follow-up observation phase of 3 weeks.

Administration of fezolinetant in the study was largely in compliance with the recommendations of the SPC [14]. Instead of the approved 45 mg film-coated tablet, 2 film-

coated tablets of 30 mg and 15 mg were used. In the comparator arm, the patients received placebo. The study was thus not designed for a comparison with watchful waiting. Since regular visits (every 2 to 4 weeks) took place in the study, this is considered to be a sufficient approximation to the ACT watchful waiting in the present therapeutic indication (see section on the DAYLIGHT study).

The primary outcomes of the study were the frequency and severity of AEs and the proportion of patients with endometrial hyperplasia or carcinoma. According to the information in Module 4 A, patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Studies 1 SKYLIGHT and 2

The studies SKYLIGHT 1 and SKILIGHT 2 are double-blind RCTs comparing fezolinetant with placebo. Both studies were planned and conducted nearly analogously. The inclusion and exclusion criteria for both studies were identical. The two studies are therefore described together below.

Women aged 40 to 65 years with moderate to severe menopause-associated vasomotor symptoms were included. According to the inclusion criteria, these patients had to have experienced an average of at least 7 to 8 moderate to severe hot flushes per day or 50 to 60 moderate to severe hot flushes per week in the last 10 days before randomization. The BMI had to be between 18 and 38 kg/m^2.

527 patients in the SKYLIGHT 1 study and 501 patients in the SKYLIGHT 2 study were randomly assigned in a 1:1:1 ratio to one of the following 3 study arms: fezolinetant 30 mg/day, fezolinetant 45 mg/day or placebo. Randomization was stratified according to smoking status (smoker vs. non-smoker). Since a fezolinetant dose of 30 mg is not covered by the approval [14], this study arm is not considered further by the company in the dossier. This approach is appropriate.

Participation in the study was not restricted to patients who were not eligible for hormone replacement therapy. The company therefore formed a subpopulation for the benefit assessment based on the 4 criteria of contraindication (without porphyria), risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy (see section on the DAYLIGHT study). The subpopulation of the SKYLIGHT 1 study analysed by the company comprised 142 patients in the fezolinetant arm and 148 patients in the placebo arm. For the SKYLIGHT 2 study, there were 145 patients in the fezolinetant arm and 149 patients in the placebo arm.

Both studies comprise a double-blind placebo-controlled phase up to Week 12 and a subsequent non-controlled extension phase. In the 40-week extension phase, patients in the

placebo arm were randomly assigned to treatment with fezolinetant (30 mg/day or 45 mg/day). Patients who were assigned to one of the two fezolinetant arms at the start of the study continued their treatment in the extension phase. The treatment period of a total of 52 weeks was followed by a 3-week follow-up phase.

Administration of fezolinetant in both studies was largely in compliance with the recommendations of the SPC [14]. Instead of the approved 45 mg film-coated tablet, 2 film-coated tablets of 30 mg and 15 mg were used, as in the DAYLIGHT 2 study. In the comparator arm, the patients received placebo. The studies were thus not designed for a comparison with watchful waiting. Since regular visits (every 2 to 4 weeks) took place in the studies, this is considered to be a sufficient approximation to the ACT watchful waiting in the present therapeutic indication (see section on the DAYLIGHT study).

The co-primary outcomes in both studies were defined as the frequency and severity of moderate to severe vasomotor symptoms at Week 4 and Week 12. According to the information in Module 4 A, patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Assessment of the evidence presented by the company

Suitability of the evidence presented by the company for research question 2

Operationalization of “hormone replacement therapy is not an option” not adequate

Research question 2 of the present benefit assessment comprises patients for whom hormone replacement therapy is not an option or who have decided against it after individual risk-benefit assessment. The company used the 4 criteria of contraindication, risk factor, discontinuation of hormone replacement therapy and the decision against hormone replacement therapy after a medical consultation to characterize this patient group (see section on the DAYLIGHT study for a detailed description). Patients were assigned to research question 2 if at least 1 criterion was fulfilled.

Research question 2 explicitly includes patients who decided against hormone replacement therapy following a risk-benefit assessment - regardless of whether the treatment was suitable for the patient or not. The criterion "decision against hormone replacement therapy after a medical consultation" defined by the company is therefore considered adequate. The same applies to the criterion “discontinuation of hormone replacement therapy”. For these patients, it can be assumed that a consultation took place before the start of hormone replacement therapy and that the discontinuation of treatment was also carried out in consultation with the attending physician.

According to the recommendations of national and international scientific societies, hormone replacement therapy should not be considered if there are contraindications such as a history

of breast cancer or another oestrogen-dependent tumour [17-19]. Unexplained vaginal bleeding, previous or existing deep vein thrombosis and arterial thromboembolic disease are also contraindications [18,19]. Further contraindications such as porphyria and hypersensitivity to oestrogen and progesterone can be found in the specifications of the SPC for hormone replacement products [20]. The criterion “contraindication” defined by the company is therefore also adequate. The situation is different for the criterion “risk factor”. According to national and international scientific societies, the risk factor of diabetes mellitus listed by the company does not represent a contraindication for hormone replacement therapy; rather, hormone replacement therapy can also be considered for these patients after an individual risk-benefit assessment [17-19]. The risk factor “hyperlipidaemia” also does not appear to be suitable for ruling out the eligibility of hormone replacement therapy in principle. For example, the S3 guideline on perimenopause and postmenopause lists the favourable effects of oral oestrogen administration on the lipid metabolism [17]. There is little or no evidence for the other risk factors mentioned by the company, so that a patient-specific decision should also be made here [17-19]. Accordingly, without further risk-benefit assessment, the risk factor “criterion” is not suitable for defining the patient population for whom hormone replacement therapy is not an option.

In the DAYLIGHT study, ineligibility for hormone replacement therapy operationalized on the basis of the 4 criteria was an inclusion criterion. The largest proportion of patients were included in the study based on the criteria “decision against hormone replacement therapy after a medical consultation” (37.2%) and “presence of a risk factor” (36.5%). 15.3% of patients belonged to the treatment group “discontinuation of hormone replacement therapy” and 11.1% had a contraindication. In principle, it was possible for patients to fulfil more than 1 criterion. According to the defined hierarchy of criteria in the statistical analysis plan, patients who had been assigned to the criterion “risk factor” could also have discontinued hormone replacement therapy and/or refused it after a medical consultation. However, it is not clear from the available data how many patients in the risk factor group fulfilled a second criterion. Although 95.1% of patients denied the question whether they would start hormone replacement therapy for their symptoms in the electronic case report form, this is not to be equated with a decision against treatment following an individual risk-benefit assessment in the sense of research question 2.

Due to the high proportion of patients with the criterion “risk factor” in combination with the lack of information on how many of the patients fulfilled a second criterion, it is not sufficiently ensured for the reasons explained above that at least 80% of the patients in the DAYLIGHT study were to be assigned to research question 2.

In the 3 SKYLIGHT studies, ineligibility for hormone replacement therapy was not an inclusion criterion for participation in the study. For the subpopulations of these studies presented by

the company, no information is available on the distribution of patients to the various criteria. For each of the 3 SKYLIGHT studies, it is therefore unclear whether at least 80% of the patients corresponded to research question 2. In addition, the SKYLIGHT studies are subject to the problems described below.

SKYLIGHT 4: No restriction to moderate to severe vasomotor symptoms

The approved therapeutic indication of fezolinetant is limited to moderate to severe vasomotor symptoms [14]. In the studies DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2, this restriction is reflected in the inclusion criteria. However, patients with vasomotor symptoms could be included in the SKYLIGHT 4 study regardless of their severity. Data on the frequency and/or severity of the vasomotor symptoms are neither available for the total population nor for the subpopulation of the SKYLIGHT 4 study presented in the dossier. For the subpopulation of the SKYLIGHT 4 study used by the company for the benefit assessment, it is unclear whether moderate to severe vasomotor symptoms were present in at least 80% of the patients and, at the same time, hormone replacement therapy was not an option.

SKYLIGHT 1 and SKYLIGHT 2: study duration too short

According to the SPC, there is no restriction on the treatment duration for fezolinetant [14]. It is therefore assumed that fezolinetant is administered for the duration of the vasomotor symptoms. In the patient population from the studies DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 presented by the company, hot flushes had been occurring for an average of 75 days. Studies show that frequent hot flushes (on more than 6 days in the last 2 weeks) and moderate to severe hot flushes last for about 4.5 years [21,22]. The duration of the symptoms therefore also supports the minimum study duration of 24 weeks chosen in this assessment.

In the studies SKYLIGHT 1 and SKYLIGHT 2, the placebo-controlled phase lasted 12 weeks in each case. The data presented for these two studies are not suitable for the benefit assessment.

Summary

The company defined the ineligibility for hormone replacement therapy on the basis of the criteria of contraindication, risk factor, discontinuation of hormone replacement therapy or decision against hormone replacement therapy, of which at least 1 criterion had to be fulfilled. As described above, hormone replacement therapy can generally also be considered in the presence of a risk factor. Therefore, this criterion is not adequate to determine an assignment to research question 2 of the benefit assessment.

For the DAYLIGHT study presented by the company and for the subpopulations of the studies SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 presented, it is therefore not sufficiently ensured that at least 80% of the patients correspond to research question 2. In addition, the studies

SKYLIGHT 1 and SKYLIGHT 2 with a comparative treatment period of 12 weeks are too short, and for the SKYLIGHT 4 study it is unclear how many patients in the subpopulation had moderate to severe vasomotor symptoms.

The data presented by the company are therefore disregarded in the benefit assessment. The patient group relevant for research question 2 of the benefit assessment comprises those patients with moderate to severe menopause-associated vasomotor symptoms who fulfil one of the criteria defined by the company: contraindication, discontinuation of hormone replacement therapy or decision against hormone replacement therapy.

Further notes on the data presented by the company

Irrespective of the fact that the analyses on the studies DAYLIGHT and SKYLIGHT 4 presented by the company are not suitable for the benefit assessment for the reasons described above, there are the following uncertainties regarding the patient-reported outcomes:

Frequency and severity of the vasomotor symptoms

As part of the studies, the patients reported the number and severity of their vasomotor symptoms on a daily basis. Thereby, the severity of the vasomotor symptoms was rated on a scale of 0 to 3 (no [0], mild [1], moderate [2] and severe [3] hot flushes). With regard to the frequency of vasomotor symptoms, the company presented analyses on the proportion of patients with a reduction by 100%, at least 75% and at least 50% in the average daily frequency of moderate and severe hot flushes compared to baseline in the dossier. Analyses on the frequency of the vasomotor symptoms of any severity (including mild hot flushes) are lacking.

Additional patient-reported outcomes

In the studies presented by the company, outcomes the on morbidity and health-related quality of life were recorded using various questionnaires, among other things. However, the company did not present the questionnaires or versions used in each case. In the dossier, the company also states, for example, that the study programme on fezolinetant used an adapted form of the Work Productivity and Activity Impairment Questionnaire to assess the effects of menopausal symptoms, but does not describe the adjustments in more detail. Without the questionnaires used, it is not possible to assess the instruments applied to record the patient-reported outcomes.

Analysis of the outcome of sleep disorders (PROMIS)

Irrespective of the limitation described above, the company based its analyses of the DAYLIGHT study on the PROMIS Sleep Disturbance Short Form 8b on the raw values and did not transform the values. For example, it determined 15% of the scale range of the raw values as the response criterion for his responder analyses. However, according to the PROMIS manual (current version: [23]), the raw values are to be converted into T-scores. In doing so,

the scale range can be taken from the PROMIS manual. Two types of scoring are described for the PROMIS short forms: Firstly, a so-called "Response Scoring Pattern", which can be calculated online via the HealthMeasures Scoring Service [24] and free of charge via tools. It uses the respective item-level parameters for each item and each answer. Alternatively, a manual conversion of the raw value into a T-Score is possible. For this purpose, PROMIS provides online conversion tables for all short forms. Both manual scoring using conversion tables and the use of the “Response Scoring Pattern” via the HealthMeasures Scoring Service utilize T-scoring. According to the PROMIS manuals, the use of the "Response Scoring Pattern" should be favoured, as it measures more accurately and deals better with missing values.

I 4.2 Results

No suitable data are available for the assessment of the added benefit of fezolinetant in comparison with the ACT in patients with moderate to severe vasomotor symptoms who are no candidates for hormone replacement therapy. There is no hint of an added benefit of fezolinetant in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of fezolinetant in comparison with the ACT in menopausal patients with moderate to severe vasomotor symptoms who are no candidates for hormone replacement therapy, the added benefit is not proven.

I 5 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of the added benefit of fezolinetant in comparison with the ACT.

Table 5: Fezolinetant – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is an option and who have decided in favour of hormone replacement therapy after an individual risk-benefit assessment[b]	Treatment of physician's choice choosing from systemic hormone replacement therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])c	Added benefit not proven
2	Menopausal women with moderate to severe vasomotor symptoms for whom hormone therapy is not an option, or those who have decided against therapy after individual risk-benefit assessment[b]	Watchful waiting	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the patients in research questions 1 and 2 are postmenopausal.
c. For the implementation of the ACT for research question 1, a single comparator study is generally not sufficient. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization).

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

For the menopausal patients with moderate to severe vasomotor symptoms covered by research question 1, for whom hormone replacement therapy is an option, the company also claims no added benefit. For research question 2, the assessment described above differs from that of the company, which derived proof of a major added benefit for menopausal patients with moderate to severe vasomotor symptoms for whom hormone replacement therapy is not an option.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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

3. Astellas Pharma Global Development. A Phase 3b, Randomized, Double-blind, Placebo-controlled, 24-week Study to Assess the Efficacy and Safety of Fezolinetant in Menopausal Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) and Considered Unsuitable for Hormone Replacement Therapy.; study 2693-CL-0312; Clinical Study Report [unpublished]. 2023.

4. Astellas Pharma Global Development. A Study of Fezolinetant to Treat Hot Flashes in Women Going Through Menopause (Daylight) [online]. 2024 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT05033886.

5. Neal-Perry G, Cano A, Lederman S et al. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A Randomized Controlled Trial. Obstet Gynecol 2023; 141(4): 737-747. https://doi.org/10.1097/aog.0000000000005114.

6. Astellas Pharma Global Development. A Study to Find Out How Safe Long-term Treatment With Fezolinetant is in Women With Hot Flashes Going Through Menopause (Skylight 4) [online]. 2023 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT04003389.

7. Astellas Pharma Global Development. A Randomized, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause; study 2693-CL-0304; Clinical Study Report [unpublished]. 2022.

8. Lederman S, Ottery FD, Cano A et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. Lancet 2023; 401(10382): 1091-1102. https://doi.org/10.1016/S0140-6736(23)00085-5.

9. Astellas Pharma Global Development. A Study to Find Out if Fezolinetant Helps Reduce Moderate to Severe Hot Flashes in Women Going Through Menopause (Skylight 1) [online]. 2023 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT04003155.

10. Astellas Pharma Global Development. A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause; study 2693-CL-0301; Clinical Study Report [unpublished]. 2022.

11. Johnson KA, Martin N, Nappi RE et al. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause: a Phase 3 RCT. J Clin Endocrinol Metab 2023; 108(8): 1981-1997. https://doi.org/10.1210/clinem/dgad058.

12. Astellas Pharma Global Development. A Study to Find Out if Fezolinetant Helps Reduce Moderate to Severe Hot Flashes in Women Going Through Menopause - 2 (Skylight 2) [online]. 2023 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT04003142.

13. Astellas Pharma Global Development. A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause; study 2693-CL-0302; Clinical Study Report [unpublished]. 2022.

14. Astellas. Veoza 45 mg Filmtabletten [online]. 2024 [Accessed: 12.04.2024]. URL: https://www.fachinfo.de/.

15. Astellas Pharma Global Development. A Study to Assess Bioequivalence of Fezolinetant Formulations in Healthy Female Participants [online]. 2022 [Accessed: 08.04.2024]. URL: https://clinicaltrials.gov/study/NCT04277624.

16. European Medicines Agency. Veoza; Assessment report [online]. 2023 [Accessed: 16.04.2024]. URL: https://www.ema.europa.eu/en/documents/assessment-report/veoza-epar-public-assessment-report_en.pdf.

17. Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe, Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe. Leitlinienprogramm: Peri- und Postmenopause - Diagnostik und Interventionen. 2020.

18. The North American Menopause S. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 2022; 29(7): 767-794. https://doi.org/10.1097/GME.0000000000002028.

19. Stuenkel CA, Davis SR, Gompel A et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100(11): 3975-4011. https://doi.org/10.1210/jc.2015-2236.

20. Novo Nordisk. Activelle [online]. 2023 [Accessed: 16.03.2024]. URL: https://www.fachinfo.de/.

21. 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.

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

23. healthMeasures. Sleep Scoring Manual [online]. 2023 [Accessed: 05.04.2024]. URL: https://www.healthmeasures.net/images/PROMIS/manuals/Scoring_Manual_Only/PROMIS_Sleep_Scoring_Manual_05Dec2023.pdf.

24. HealthMeasures. HealthMeasures Scoring Service powered by Assessment Center; An application to score PROMIS, NIH Toolbox, and Neuro-QoL instruments [online]. [Accessed: 05.04.2024]. URL: https://www.assessmentcenter.net/ac_scoringservice/.

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