SMC2898

fezolinetant film-coated tablets (Veoza®)

Astellas Pharma Ltd

05 June 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

fezolinetant (Veoza®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

SMC restriction: for use in patients for whom hormone replacement therapy (HRT) is not deemed suitable.

In a phase IIIb study fezolinetant significantly reduced the frequency of VMS in menopausal participants considered unsuitable for hormone therapy compared with placebo. In addition, in two identical phase III studies fezolinetant significantly reduced the frequency and severity of VMS compared with placebo in menopausal participants.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Fezolinetant is a non-hormonal selective neurokinin 3 (NK3) receptor antagonist that inhibits neurokinin B binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron. This is believed to modulate neurological changes in KNDy activity in the thermoregulatory centre of the hypothalamus which are thought to have a causal effect on vasomotor symptoms (VMS) associated with menopause.[1]

The recommended dose is 45 mg taken orally once daily. Benefit of long-term treatment should be periodically assessed since the duration of VMS can vary by individual. See the summary of product characteristics (SPC) for further details.[1]

1.2. Disease background

Vasomotor symptoms (VMS), including hot flushes and night sweats, are the most common menopausal symptom and affect 70% to 80% of individuals. They are characterised by a sudden sensation of spreading heat originating in the upper chest and face which typically last for two to four minutes and can cause profuse perspiration and occasionally palpitations, they are sometimes followed by chills and a feeling of anxiety. Although the frequency and duration of VMS vary between people, they are more common at night and can range from one to two daily to one per hour during the day and night. They can have a significant impact on quality of life affecting physical and mental health and can also interfere with working life. They can persist for a median of 3.4 years and have been reported as moderate to severe in 25% of cases in those aged between 50 to 55 years. The exact pathophysiology of VMS is unknown; however, changes in hormone levels, alterations in the central thermoregulatory zone, alterations in the release of neurotransmitters, genetic predisposition and social or cultural factors may all contribute.[2-5]

1.3. Company proposed position

The submitting company has requested that SMC considers fezolinetant for use in patients for whom hormone replacement therapy (HRT) is not deemed suitable, who may be further subdivided into:

- HRT-contraindicated: menopausal women for whom HRT is contraindicated, including due to venous thromboembolism, cardiovascular disease, metabolic syndrome, severe hypertension, uncontrolled/complex diabetes mellitus, porphyria, etc.
- HRT-caution: menopausal women for whom medical risk assessment of the specific caution has concluded that the risk of HRT outweighs the likely benefit.
- HRT-stoppers: menopausal women who have previously received HRT but no longer take HRT.
- HRT-averse: menopausal women who do not want to take hormones.

1.4. Treatment pathway and relevant comparators

Options for menopausal symptom control include pharmacological and non-pharmacological treatments and are person specific. The first line pharmacological treatment for the management

of VMS is HRT with a combined oestrogen and progestogen or an oestrogen only product. However, some people may choose not to take HRT because it is not recommended due to individual risk factors (for example, in people with breast or hormone sensitive cancers), personal choice or they have been unable to tolerate it. Alternative non-hormonal pharmacological treatments that may be used for symptom control are limited, these include clonidine, selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline re-uptake inhibitors (SNRIs), gabapentin, pregabalin and oxybutynin. These non-hormonal options are used off-label, apart from clonidine, which is licensed for the management of vasomotor conditions commonly associated with the menopause and characterised by flushing. Cognitive behavioural therapy is recommended in guidelines as a non-pharmacological treatment option for the management of symptoms associated with menopause. Other treatments include natural health products, herbal treatments and complementary therapies however there is often limited or no evidence for their efficacy and safety in treating menopause related symptoms.[4, 6-8]

For the proposed positioning, no active treatment was the most relevant comparator according to the submitting company and clinical experts consulted by SMC. Some clinical experts indicated that clonidine and other non-hormonal treatments used off-label, such as SSRIs, would potentially be treatment options for some patients although use may be limited by lack of efficacy or side effects.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of fezolinetant is from the DAYLIGHT and SKYLIGHT studies as detailed in Table 2.1.

Table 2.1: Overview of relevant studies

Criteria	DAYLIGHT[9]	SKYLIGHT 1 and 2[10, 11]
Study design	Multicentre, randomised, double-blind phase IIIb study	Multicentre, randomised, double-blind 12-week phase III studies, followed by a non-controlled extension period of 40 weeks.
Eligible patients	• Born female patients aged ≥40 years and ≤65 years • Confirmed as menopausal per one of the following criteria: spontaneous amenorrhoea for ≥12 consecutive months or spontaneous amenorrhoea for ≥6 months with biochemical criteria of menopause (follicle-stimulating hormone >40 IU/L) or bilateral oophorectomy ≥6 weeks prior to the screening visit (with or without hysterectomy) • VMS and unsuitable to receive HRT: ○ HRT-contraindicated: undiagnosed vaginal bleeding; history of breast cancer or oestrogen dependent tumours; arterial thromboembolic disease, venous thrombophilic disorder;	• Born female patients aged ≥40 and ≤65 years • Body mass index 18 kg/m^2 to 38 kg/m^2 • VMS related to menopause and with spontaneous amenorrhoea for ≥12 consecutive months; or ≥6 months with biochemical criteria for menopause (follicle-stimulating hormone >40 IU/L); or bilateral oophorectomy ≥6 weeks before screening • At least 7 to 8 moderate to severe hot flushes (VMS) each day or 50 to 60 per week, within 10 days prior to randomisation • Normal, negative or no clinically significant

	hypersensitivity to oestrogen and progesterone therapy or any of the excipients; porphyria ○ HRT-caution: a history of diabetes mellitus, hyperlipidaemia; current smoker; migraine, obesity; systemic lupus erythematosus, epilepsy; family history of breast cancer in the first degree relative or mutation of breast cancer gene (*BRCA1* and *BRCA2*) ○ HRT-stoppers: lack of efficacy; HRT-related side effects; advised by healthcare provider to stop due to length of time on HRT or due to patient's age ≥60 years old ○ HRT-averse: made an informed choice to not take HRT after a consultation about the benefits and risks of HRT • Minimum average of 7 moderate to severe events of VMS per day as recorded in the electronic diary during the last 10 days prior to randomisation.	findings on mammogram within 12 months of screening • Normal or clinically non-significant Papanicolaou test results within 12 months of screening • Willingness to undergo transvaginal ultrasound to evaluate the uterus and ovaries at screening and at 52 weeks or early discontinuation • Willingness to undergo endometrial biopsy at screening and at week 52, with exception of people who have had a supracervical or full hysterectomy • Willingness to under endometrial biopsy in case of uterine bleeding or early discontinuation of the study or study drug
Treatments	Fezolinetant 45 mg orally once daily or placebo for 24 weeks.	Fezolinetant 30 mg, fezolinetant 45 mg or placebo orally once daily for 12 weeks. Following this, participants in the placebo group could crossover and were re-randomised to receive fezolinetant 30 mg or 45 mg in a 40-week active treatment extension period. Only results from the licensed 45 mg dose will be included in this submission.
Randomisation	Equal randomisation stratified according to smoking status (current or non-smoker [former or never])	Equal randomisation stratified according to smoking status (active smoker or non-smoker)
Primary outcome	Mean change in the frequency of moderate-severe VMS from baseline to week 24.	There were four co-primary outcomes: mean change in frequency of moderate to severe VMS from baseline to week 4 and from baseline to week 12, and mean change in severity of moderate to severe VMS from baseline to week 4 and from baseline to week 12.
Selected Secondary outcomes	Mean change in severity of moderate to severe VMS from baseline to week 24	Mean change in the PROMIS SD-SF 8b total score from baseline to week 12
Statistical analysis	The primary analysis in all studies was conducted in the FAS which included all patients that underwent randomisation and received at least one dose of study medication. A hierarchical statistical testing strategy was applied in the studies with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported)	
Abbreviations: FAS=full analysis set; HRT = hormonal replacement therapy; IU = international units; PROMIS SD-SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b; VMS = vasomotor symptoms.		

In the DAYLIGHT study, fezolinetant was associated with statistically significant improvements in the frequency and severity of VMS at week 24 compared with placebo. The results have been detailed in Table 2.2.[9] The full analysis set represent the proposed positioning by the submitting company, in people deemed unsuitable for HRT.

Table 2.2: Primary and selected secondary outcomes from DAYLIGHT in the FAS.[9]

	Fezolinetant (n= 226)	Placebo (n= 226)
Primary outcome: daily frequency of moderate to severe VMS from baseline to week 24		
Baseline, mean daily events	10.58	10.75
LS mean change at week 24	-8.13	-6.20
LS mean difference, (95% CI)	-1.93 (-2.64 to -1.22), p<0.001	
Secondary outcome: daily severity of moderate to severe VMS from baseline to week 24		
Baseline, mean severity	2.43	2.41
LS mean change at week 24	-1.01	-0.62
LS mean difference, (95% CI)	-0.39 (-0.57 to -0.21), p<0.001	
Secondary outcome: change in PROMIS SD-SF 8b total score from baseline to week 24[A]		
Baseline, mean score	28.3	27.6
LS mean change at week 24	-7.0	-4.5
LS mean difference, (95% CI)[B]	-2.5 (-3.9 to -1.1)	

Abbreviations: CI=confidence interval; FAS=full analysis set; LS= least squares; PROMIS SD-SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b; SD=standard deviation; VMS=vasomotor symptoms. [A]PROMIS SD-SF 8b assesses self-reported sleep disturbance over the past 7 days for 8 items: perceptions of restless sleep; satisfaction with sleep; refreshing sleep; difficulties sleeping, getting to sleep or staying asleep; amount of sleep; and sleep quality. Scores for each item range from 1 to 5 and total scores from 8 to 40. Higher scores indicate a more disturbed sleep. [B]Not controlled for multiplicity therefore p-value not reported.

Additional data are available from the SKYLIGHT 1 and SKYLIGHT 2 studies; these were conducted in a wider population and reflect the full licensed indication. In both studies treatment with fezolinetant significantly reduced the frequency and severity of VMS compared with placebo. There was also a statistically significant reduction in sleep disturbance associated with fezolinetant compared with placebo in SKYLIGHT 2.[8, 10, 11] The results have been detailed in Table 2.3.

Table 2.3: Primary and selected secondary outcomes for SKYLIGHT 1 and SKYLIGHT 2 in the FAS [8, 10-12]

	SKYLIGHT 1		SKYLIGHT 2	
	Fezolinetant 45 mg (n= 174)	**Placebo (n= 175)**	**Fezolinetant 45 mg (n= 167)**	**Placebo (n= 167)**
Co-Primary outcome: daily frequency of moderate to severe VMS from baseline to week 4 and 12				
Baseline, mean daily events	10.4	10.5	11.8	11.6
LS mean change at week 4	-5.39	-3.32	-6.26	-3.72
LS mean difference at week 4, (95% CI)	-2.07 (-2.89 to -1.25), p<0.001		−2.55 (−3.45 to −1.64), p<0.001	
LS mean change at week 12	-6.44	-3.9	-7.50	-4.97
LS mean difference at week 12, (95% CI)	-2.55 (-3.40 to -1.70), P<0.001		−2.53 (-3.60 to -1.46), p<0.001	

Co-Primary outcome: daily severity of moderate to severe VMS from baseline to week 4 and 12				
Baseline, mean severity	2.4	2.4	2.4	2.4
LS mean change at week 4	-0.46	-0.27	-0.61	-0.32
LS mean difference at week 4, (95% CI)	−0.19 (−0.30 to −0.07), p=0.002		−0.29 (−0.41 to −0.16), p<0.001	
LS mean change at week 12	-0.57	-0.37	-0.77	-0.48
LS mean difference at week 12, (95% CI)	-0.20 (−0.35 to −0.06), p=0.007		−0.29 (−0.45 to −0.13), P<0.001	
Secondary outcomes: change in PROMIS SD-SF 8b total score from Baseline to week 12[A]				
Baseline, mean score	27.1	26.4	26.2	27.4
LS mean change at week 12	-4.2	-3.2	-5.5	-3.4
LS mean difference, (95% CI)	−1.1 (−2.5 to 0.4), p=0.155		−2.0 (−3.5 to −0.6), p=0.007	

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; LS = least squares; PROMIS SD-SF 8b = Patient-reported Outcomes Measurement Information System Sleep Disturbance–Short Form 8b; SD = standard deviation; VMS = vasomotor symptoms [A]PROMIS SD-SF 8b assesses self-reported sleep disturbance over the past 7 days for 8 items: perceptions of restless sleep; satisfaction with sleep; refreshing sleep; difficulties sleeping, getting to sleep or staying asleep; amount of sleep; and sleep quality. Scores for each item range from 1 to 5 and total scores from 8 to 40. Higher scores indicate a more disturbed sleep.

For this resubmission, the clinical evidence from DAYLIGHT, SKYLIGHT 1 and 2 informing the economic base case were updated and based on responder analysis of change from baseline in moderate to severe VMS frequency (defined as a reduction of ≥75% in moderate to severe VMS frequency at week 12). This was chosen as clinical experts consulted by the submitting company considered this to be a more objective outcome than measures of severity and that a 75% threshold was clinically meaningful.

Table 2.4: Responders with ≥75% reduction in moderate to severe VMS at week 12 from DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 in the FAS [13]

Study	**Responders with ≥75% reduction in moderate to severe VMS at week 12**	
	Fezolinetant	**Placebo**
DAYLIGHT	110/226 (49%)	66/226 (29%)
	OR (95% CI): 2.30 (1.56 to 3.40)	
SKYLIGHT 1	60/174 (35%)	23/175 (13%)
	OR (95% CI): 3.48 (2.05 to 6.06)	
SKYLIGHT 2	66/167 (40%)	35/167 (21%)
	OR (95% CI): 2.48 (1.53 to 4.09)	

Abbreviations: CI = confidence interval; OR = odds ratio; VMS = vasomotor symptoms.

2.2. Evidence to support the positioning proposed by the submitting company

The DAYLIGHT study described above provides evidence to support the proposed positioning. In addition, the submitting company provided pooled analyses of SKYLIGHT 1 and SKYLIGHT 2 in a subpopulation of patients that were not suitable for HRT. In these analyses, fezolinetant was associated with a reduction in daily frequency of VMS compared with placebo from baseline to week 4 and to week 12. Pooled data from this subpopulation were also available for the active extension phase of the SKYLIGHT studies and indicated a reduction in daily frequency of VMS with fezolinetant from baseline to week 24 and to week 52.[12]

*Other data were also assessed but remain confidential.**

2.3. Health-related Quality of Life outcomes

In DAYLIGHT, health related quality of life was assessed using Patient Global Impression (PGI) scales, Menopause-specific Quality of Life (MENQOL) questionnaires, Work Productivity and Activity Impairment questionnaire specific to VMS (WPAI-VMS) and the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) version utility scores and visual analogue scale (VAS). The MENQOL evaluates four domains of menopausal symptoms including vasomotor, psychosocial, physical and sexual, the total score ranges from 0 (not bothersome) to 6 (extremely bothersome). At week 24, there was a greater numerical reduction from baseline in the MENQOL total score in the fezolinetant group compared with placebo; -1.66 and -1.22 in each group respectively. The PGI scale evaluates changes in VMS (PGI-C VMS) and sleep disturbance (PGI-C SD) and are measured on a scale of 1 (much better) to 7 (much worse); change in severity of sleep disturbance (PGI-S SD) is measured on a scale of 1 (no problems) to 4 (severe problems). At week 24, a numerically greater proportion of participants in the fezolinetant group reported improvements in PGI-C VMS, PGI-C SD and PGI-S SD compared with placebo. The WPAI-VMS measures VMS related work productivity and activity across four domains: absenteeism, presenteeism, overall work productivity loss and activity impairment. At week 24, improvements were observed in the fezolinetant group compared with placebo in all domains except absenteeism. At weeks 4, 12, 16 or 24 there were no differences in change from baseline between groups for any EQ-5D-5L dimensions or on the VAS.[14]

In SKYLIGHT 1 and 2, at week 12 there were improvements observed in the fezolinetant group compared with placebo across all four domains in MENQOL, all WPAI-VMS domains except absenteeism (in SKYLIGHT 1) and in SKYLIGHT 2 an improvement in EQ-5D-5L VAS but no between-group difference in EQ-5D-5L dimension scores.[8]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing fezolinetant with non-hormonal comparators (which is a relevant comparator for some patients) in patients with moderate to severe VMS associated with menopause who are not deemed suitable for HRT, the submitting company presented two network meta-analyses (NMAs). The first NMA was conducted for response which compared fezolinetant with desvenlafaxine and placebo, and the second NMA was conducted for treatment discontinuation for fezolinetant compared with paroxetine, desvenlafaxine and placebo. These were used to inform the economic base case. Details are presented in Table 2.5.

Table 2.5: Summary of indirect treatment comparisons

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Design</td><td>Two NMAs</td></tr>
<tr><td>Population</td><td>Patients with moderate to severe VMS associated with menopause who are not deemed suitable for HRT</td></tr>
<tr><td>Comparators</td><td>Desvenlafaxine and paroxetine</td></tr>
<tr><td>Studies included</td><td>Response outcome: Speroff [15], Pinkerton [16], Archer [17, 18], Bouchard [19], Pooled SKYLIGHT [20, 21], DAYLIGHT [9]

Discontinuation outcome: Speroff [15], Pinkerton [16], Archer [17, 18], Pooled SKYLIGHT [20, 21], DAYLIGHT [9], Simon [22]</td></tr>
<tr><td>Outcomes</td><td>• Response: ≥75% reduction in frequency of moderate to severe VMS at week 12.
• Discontinuation: all-cause treatment discontinuation assessed at week 12.</td></tr>
<tr><td>Results</td><td>The point estimates for response favoured fezolinetant, however the 95% credible intervals crossed one in the comparisons versus desvenlafaxine suggesting no evidence of a difference between these treatments. Discontinuation favoured fezolinetant versus all comparators, however the credible intervals were wide.

<table>
<tr><th>Outcome</th><th>Comparator</th><th>Relative treatment estimate, OR (95% CrI)</th></tr>
<tr><td rowspan="3">Percentage reduction (≥75%) in frequency of moderate to severe VMS at week 12</td><td>Desvenlafaxine 50 mg</td><td>0.46 (0.14 to 1.69)</td></tr>
<tr><td>Desvenlafaxine 100 mg</td><td>0.84 (0.35 to 2.09)</td></tr>
<tr><td>Placebo</td><td>0.39 (0.19 to 0.84)</td></tr>
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Abbreviations: CrI = credible interval; HRT = hormone replacement therapy; NMA = network meta-analysis; OR = odds ratio; VMS = vasomotor symptoms.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the DAYLIGHT and SKYLIGHT studies, fezolinetant was compared with placebo; the submitting company considered placebo a proxy for no active treatment which is the most relevant comparator.[9-11] In the DAYLIGHT study, the median duration of treatment in both groups was 168 days. Any treatment-related adverse event (TRAE) was reported by 17% (39/226) of patients in the fezolinetant group and 11% (25/226) in the placebo group, these were considered serious in 0.4% versus 0, and patients discontinuing therapy due to a TRAE was 3.1% in both groups.[9] In the SKYLIGHT 1 and SKYLIGHT 2 studies, the median duration of treatment during the double-blind

period was 84 days in both the fezolinetant and placebo groups. TRAEs were reported by 8% (13/173) and 15% (25/167) in the fezolinetant 45 mg groups and 13% (22/175) and 6.6% (11/167) in the placebo groups in SKYLIGHT 1 and SKYLIGHT 2 respectively. The safety profile in both studies was similar to DAYLIGHT with most TRAEs mild to moderate in severity and a low frequency of discontinuations due to TRAEs.[10, 11]

The regulator noted that fezolinetant was generally well-tolerated and adverse events affecting >5% of participants were generally low across studies and included headache, upper respiratory tract infection, nausea, fatigue, nasopharyngitis and raised blood glucose. Elevated liver function tests (LFTs) have been reported during treatment with fezolinetant; it should not be used in patients with known liver disease or at high risk of liver disease. LFTs should be checked before and during treatment to monitor for drug induced liver injury. See the SPC for further safety information.[1, 8, 23]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Fezolinetant is the first NK3 receptor antagonist licensed for the treatment of moderate to severe VMS associated with menopause. In those unsuitable for HRT, current treatment options are limited and therefore in this population of patients, fezolinetant could fill an unmet need.
- In the phase IIIb DAYLIGHT study, compared with placebo, treatment with fezolinetant led to a statistically significant reduction in the frequency and severity of VMS associated with menopause in people unsuitable for HRT at 24 weeks. The reduction in frequency of daily VMS events compared with placebo was approximately 2; an improvement of ≥2 VMS per day has been described as clinically meaningful by the regulator. The full population of this study matches the proposed positioning.[8, 9]
- This was supported by results from the well conducted phase III SKYLIGHT 1 and 2 studies which also reported statistically significant and clinically relevant reductions in the frequency and severity of VMS associated with menopause in the fezolinetant groups compared with placebo at 4 and 12 weeks.[8, 10, 11]
- Additional evidence to support the positioning from a pooled subpopulation of participants deemed unsuitable for HRT from the SKYLIGHT 1 and SKYLIGHT 2 studies was consistent with the full population. Results from the fezolinetant group during the active extension period indicated that the reduction in VMS was sustained at 24 and 52 weeks.[12]

4.2. Key uncertainties

- In the absence of direct evidence versus non-hormonal comparators (which is a relevant comparator for some patients), the submitting company conducted two NMAs. While generally well conducted, the analyses had several limitations including reliance on an outdated literature search, unreported methods and data supporting the pooled SKYLIGHT analyses, imbalances in study population, limited data, and lack of long-term data. Uncertainties around comparators included missing comparators (such as clonidine), desvenlafaxine was used as a proxy for venlafaxine, and the paroxetine dose was lower than

that recommended by the British Menopause Society (BMS) guidance [6], limiting generalisability to the Scottish population. The company did not provide an overall conclusion, and due to these limitations, the NMA results are uncertain.

- There are limitations with the studies that may affect the generalisability to patients in NHSScotland. People recruited to the DAYLIGHT and SKYLIGHT 1 and 2 studies had at least 7 moderate to severe daily VMS events; however, in practice people with fewer or more persistent VMS may also request treatment and there is no evidence for fezolinetant in these populations. The studies did not include perimenopausal women and therefore evidence is in those who are postmenopausal only.[8-11, 24]
- Evidence to support the proposed positioning is from the full population of the DAYLIGHT study with controlled data up to 24 weeks and from a pooled subpopulation of SKYLIGHT 1 and 2 in participants unsuitable for HRT with uncontrolled evidence from 24 to 52 weeks. Therefore, there is no comparative evidence to support the proposed positioning beyond 24 weeks and relative efficacy beyond this is uncertain. There is limited evidence for the efficacy and safety of fezolinetant beyond 1 year which is relevant as VMS can last up to approximately 7 years for some people.[9-11]
- Patients with previous breast cancer or oestrogen dependent tumours and no longer on anticancer therapy were not included in the SKYLIGHT studies and very few were included in DAYLIGHT. Therefore, there is very limited evidence in this patient population and the SPC states that a decision to treat these patients with fezolinetant should be based on a benefit risk consideration with the individual. [1]
- Fezolinetant is not recommended in people receiving anticancer therapy for breast or oestrogen dependent cancers as they were not included in the studies and efficacy and safety is unknown. This may be an area of unmet need as guidelines recommend HRT is stopped in those diagnosed with breast cancer. A phase III study (HIGHLIGHT 1) is ongoing to assess the efficacy and safety of fezolinetant for the treatment of VMS in those with hormone receptor-positive breast cancer who are receiving adjuvant endocrine therapy.[1, 7, 25]

*Other data were also assessed but remain confidential.**

4.3. Clinical expert input

Clinical experts consulted by SMC considered that fezolinetant is a therapeutic advancement because of its novel mechanism of action and beneficial results observed in the phase III studies. They consider that fezolinetant fills an unmet need as an alternative non-hormonal treatment for the management of VMS in those unsuitable for HRT since current treatment options can have limited efficacy, poor tolerability or are used off-label. They indicated that its place in therapy would be for those requesting treatment for VMS who are unsuitable for HRT.

4.4. Service implications

The availability of fezolinetant as a new licensed treatment where current options are limited may increase demand for clinician appointments. LFTs need to be monitored in all patients prior to treatment initiation, during the first three months of treatment and periodically thereafter based on clinical judgement.[23]

5. Summary of Patient and Carer Involvement

We received a patient group submission from Menopause Warriors Scotland Charity, a summary of which was presented at the SMC committee meeting for the original submission. Menopause Warriors Scotland Charity is a registered charity and has not received any pharmaceutical company funding in the past two years.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

Table 6.1: Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	10-year time horizon
Population	Menopausal women with moderate to severe VMS for whom HRT is not deemed suitable (HRT-unsuitable population)
Comparators	No active treatment (placebo) was the main comparator, with additional comparison to desvenlafaxine, used as a proxy for venlafaxine to represent off-label SSRI/SNRIs use in NHS clinical practice.
Model description	A cohort-based Markov model was used with a 4-week cycle length, structured around response-based health states (pre-response, responder, non-responder, off-treatment with VMS, VMS cessation and death). Patients who received fezolinetant or desvenlafaxine could transition between on treatment (responder/non-responder) and off-treatment health states following discontinuation, whereas patients in the no active treatment arm were allocated to responder and non-responder without treatment-related transitions.
Clinical data	Pooled direct evidence from three phase III randomised controlled studies (DAYLIGHT, SKYLIGHT 1 and 2) were used to inform both fezolinetant and no active treatment responder outcomes used in the cost-effectiveness model. Response was defined as a ≥75% reduction in VMS frequency and discontinuation rates were also sourced from the pooled data up to week 24. The odd ratios produced from the NMA for response and discontinuation were applied to the fezolinetant arm to estimate the relative treatment effect for desvenlafaxine.
Extrapolation	Patients were allocated to responder or non-responder health states at the week 12 assessment based on response rates derived from pooled DAYLIGHT and SKYLIGHT 1 and 2 data for fezolinetant and no active treatment arms. The relative effects for desvenlafaxine were informed by the odds ratios from the NMA. Prior to the week 12 assessment, discontinuation was based on pooled study data (weeks 0-12) for fezolinetant and no active treatment. Post-week 12 discontinuation rates were informed by pooled week 12-24 study data and assumed constant over time. Discontinuation for desvenlafaxine was estimated by applying the odds ratio to fezolinetant rates. At week 12, 50% of non-responders in the fezolinetant and desvenlafaxine arms are assumed to discontinue treatment, and transition to the off-treatment (with VMS) health state. At week 52, all patients who remain in the non-responder health state were assumed to discontinue treatment. Over the longer term, patients transitioned to VMS cessation at a constant rate over time, informed by Avis (2015) [5], with a mean duration of symptoms of approximately 3.4 years.

	Background mortality was applied based on general population mortality rates for women in Scotland.
Quality of life	Utility values were derived from EQ-5D-5L data collected in DAYLIGHT and SKYLIGHT 1 and 2 studies were mapped to EQ-5D-3L and applied by health state and treatment arm (treatment-dependent). Pre-response utility values were based on data from weeks 0-12 for both the fezolinetant and no active treatment arms. Post-response utilities were informed by data from weeks 0-52 for fezolinetant and weeks 0-24 for no active treatment. Utility values for desvenlafaxine were estimated as the mean of fezolinetant and no active treatment utilities. Adverse event disutilities were also included and sourced from the literature.
Costs and resource use	Medicine acquisition, monitoring (including liver function testing), healthcare resource use, and adverse events costs were included in the model.
PAS/contract price	No Patient Access Scheme (PAS) was proposed by the company.

6.2. Results

Table 6.2 displays the cost-effectiveness results.

Table 6.2: Base case results

Technologies	Total Costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Fezolinetant	£2,103	6.87	-	-	-
No Treatment	£1,633	6.82	£470	0.05	£10,031
Desvenlafaxine	£1,511	6.84	£592	0.03	£17,741

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr. = incremental; LYG: life years gained; QALYs: quality-adjusted life years.

The key QALY drivers versus no active treatment primarily came from greater QALYs generated in the responder and not on treatment with VMS health states for fezolinetant, which was then offset by the large QALYs gained in the non-responder health state in the no active treatment arm. The higher QALYs generated in the responder health state was driven by the improved responder rates for fezolinetant and longer mean time on treatment.

The key QALY drivers versus desvenlafaxine were driven by greater QALYs generated in the responder health state for fezolinetant, which were offset by the greater QALYs generated in the not on treatment (with VMS) health state for desvenlafaxine. This offset was driven by higher discontinuation rates for desvenlafaxine.

The key cost drivers were the higher medicine acquisition costs for fezolinetant versus no active treatment and desvenlafaxine, slightly offset by the higher resources use costs for the comparators in the non-responder (for no active treatment) and off treatment with VMS (for desvenlafaxine).

6.3. Sensitivity analyses

The company presented a range of sensitivity analyses including probabilistic, deterministic and scenario analysis. The one-way sensitivity analyses indicated that most influential parameters for fezolinetant versus no active treatment were utility values for the fezolinetant responder health state and no active treatment non-responder health state followed by the fezolinetant responder rates; for fezolinetant versus desvenlafaxine the incremental cost-effectiveness ratio (ICER) was

most sensitive to the responder OR for desvenlafaxine (from the NMA) and utility values for the fezolinetant responder health state.

Table 6.3: Selected scenario analysis for fezolinetant versus no active treatment and desvenlafaxine

#	Parameter	Base case	Scenario	ICER (£/QALY) versus no active treatment	ICER (£/QALY) versus desvenlafaxine
Base case				£10,031	£17,741
1	Baseline age	Mean age of menopause onset in the UK	DAYLIGHT	£10,092	£17,846
2			Pooled DAYLIGHT and SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation)	£10,045	£17,769
3	Partial responder health state (defined as 50-75% reduction in VMS frequency)	Excluded	Included (by including a partial responder health state, the stopping rules were removed)	£9,334	£16,559
4	Response assessment timepoint	Week 12	Week 4	£9,387	£17,558
5			Week 24	£11,394	£18,246
6	Response definition	75% reduction in VMS frequency	50% reduction in VMS frequency	£11,387	£19,574
7			PGI-C response	£10,897	£19,258
8	Response data source	Pooled DAYLIGHT and SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation)	Pooled SKYLIGHT 1 and 2 (HRT-unsuitable)	£9,810	£17,453
9			DAYLIGHT	£10,540	£18,361
10	Fezolintentant discontinuation rate source	Pooled DAYLIGHT and SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation)	DAYLIGHT	£9,959	£17,329
11	Fezolinetant week 24+ discontinuation rate source	Pooled DAYLIGHT and SKYLIGHT 1 and 2 Week 12–24	Pooled SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation) week 24-52	£10,105	£17,906
12	Desvenlafaxine discontinuation	OR applied to fezolinetant (NMA)	Bouchard *et al.*, (2012)	-	£12,073
13	Utility data source	Pooled DAYLIGHT and SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation)	DAYLIGHT Pre-response: Week 0–12 (fezolinetant and no treatment)	£10,301	£18,228

		Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 0–52 (fezolinetant) and week 0–24 (no active treatment)	Post response: Week 12–24 (fezolinetant and no active treatment)		
14			Pooled SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 12–52 (fezolinetant) and week 0–12 (no active treatment)	£9,716	£17,171
15			Pooled SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation) Pre-response: Week 0–12 (fezolinetant and no active treatment) Post response: Week 0–52 (fezolinetant) and week 0–12 (no active treatment)	£9,840	£17,395
16	Post responder assessment utility data source	Pooled DAYLIGHT and SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation) - Week 0–52: fezolinetant - Week 0–24: no active treatment	Pooled DAYLIGHT and SKYLIGHT 1 and 2 (HRT-unsuitable subpopulation) Week 12–52 (fezolinetant) Week 0–12 (no active treatment)	£9,717	£17,170
17	Desvenlafaxine utility source	Average of fezolinetant and no active treatment utilities	Aligned with fezolinetant utilities	-	£25,242
18	Fezolinetant monitoring cost	Include	Exclude	£9,908	£17,568

19	Additional appointments for liver testing	Exclude	Include	£10,236	£18,029
20	Adverse events	Include disutilities	Exclude disutilities	£9,762	£19,057
21		3-week duration of AEs	1-week duration of AEs	£9,850	£18,597
22		Include AE costs	Exclude AE costs	£9,966	£18,018
23	Duration of VMS data source	Avis *et al.*, (2015): postmenopausal women with VMS	Avis *et al.*, (2015): all women with VMS	£9,274	£16,098
24	Non-responder stopping rule	50% of non-responders discontinue treatment at Week 12	No stopping rule	£17,134	£24,484
25		50% of non-responders discontinue treatment at Week 12	100% of non-responders discontinue treatment at Week 12	£8,069	£15,768
26		Desvenlafaxine, 75% moderate to severe VMS frequency reduction, 50% of non-responders discontinue treatment at Week 12	Paroxetine, 50% moderate to severe VMS frequency reduction, 100% of non-responders discontinue treatment at Week 12	-	£20,312
27	Combined scenario	Combined scenario of 17 and 24		-	£35,345
28	Combined scenario	Combined scenario 3 and 17		£9,334	£22,221

Abbreviations: AE: adverse event; HRT: hormone replacement therapy; ICER: incremental cost-effectiveness ratio; OR: odds ratio; QALY: quality-adjusted life years; VMS: vasomotor symptoms.

6.4. Key strengths

- The analysis was informed by phase III randomised controlled study data comparing fezolinetant with no active treatment.
- The assumptions applied for mortality and natural cessation of VMA were considered appropriate.
- Relevant costs, including liver monitoring, were included in the model.

6.5. Key uncertainties

- There was uncertainty around the relative treatment effect estimates for desvenlafaxine derived from the NMA for both response and discontinuation. The credible intervals were wide and not statistically significant, and the evidence base was limited, resulting in uncertainty in the estimated odds ratios used in the model. Additionally, desvenlafaxine was not licensed in the UK and was used as a proxy for venlafaxine, introducing uncertainty

regarding its relevance to UK clinical practice. Clonidine, the only non-HRT treatment licensed for this indication in the UK, was not included in the NMA or economic analysis.

- The health states differed between active treatment arms and the no active treatment arms. The model may have favoured the active treatment arms by allowing partial improvement to be recognised explicitly in the active treatment arms but not symmetrically in the no active treatment arm. This lack of symmetry may have resulted in additional benefits captured in the active treatment arms. However, the inclusion of a partial responder health state (scenario 3), had limited impact on the ICER. The company provided results for a weighted comparator, which was not considered appropriate for inclusion due to the uncertainty in the assumed treatment mix and the structural asymmetry in health states between desvenlafaxine and no active treatment.
- Uncertainty was associated with the use of treatment-dependent utility values, which were applied by health state and treatment arm, resulting in different utilities being assigned to similar health states across comparators. This approach may have led to double counting of treatment benefit, as improvements were already captured both through response and discontinuing rates. Scenario 16 showed that applying treatment-independent utilities for the active treatment arms increased the ICER versus desvenlafaxine, suggesting sensitivity to this assumption.
- Stopping rules were applied at week 12 and week 52 for active treatments to determine treatment continuation for non-responders. These rules were based on assumptions rather than empirical data and determined the duration of treatment. Scenario 23 demonstrated that removing the week 12 stopping rule increased the ICERs against both comparators, indicating sensitivity to this assumption. However, SMC's clinical experts considered that the stopping rule assumptions appeared reasonable.

7. Conclusion

After considering all the available evidence, the Committee accepted fezolinetant for restricted use in NHSScotland.

8. Guidelines and Protocols

National Institute for Health and Care Excellence (NICE) published: Menopause: identification and management (NICE guideline 23) in November 2015 and this was last updated in November 2024.[4]

The British Menopause Society published a consensus statement: Non-hormonal-based treatments for menopausal symptoms and this was last reviewed in November 2025.[6]

9. Additional Information

9.1. Product availability date

16 January 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
fezolinetant	**45 mg orally once daily**	**582**

Costs from BNF online 03 April 2026.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 48,634 patients eligible for treatment with fezolinetant in year 1 and 50,191 year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 May 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.