SMC2798

fezolinetant film-coated tablets (Veoza®)

Astellas Pharma Ltd

06 June 2025

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

ADVICE: following a full submission

fezolinetant (Veoza®) is not recommended for use within NHSScotland.

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

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.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The submitting company has indicated their intention to make a resubmission.

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 life affecting physical and mental health and can also interfere with working life. They can persist for a median of 7.4 years and have been reported as moderate to severe in 25% of 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. [2-4]

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.[4-7] The submitting company considered that no active treatment was the most relevant comparator for fezolinetant based on the proposed positioning. Clinical experts consulted by SMC 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[8]	SKYLIGHT 1 and 2[9, 10]
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; hypersensitivity to oestrogen and progesterone therapy or any of the excipients; porphyria	• Born female patients aged ≥40 and ≤65 years • Body mass index 18kg/m^2 to 38kg/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 findings on mammogram within 12 months of screening

	○ 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.	• 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.
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.[8] The full analysis set represent the proposed positioning by the submitting company, in people deemed unsuitable for HRT.

Table 2.2 Primary and select secondary outcomes from DAYLIGHT in the FAS.[8]

	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.[7, 9, 10] The results have been detailed in Table 2.3.

Table 1.3 Primary and select secondary outcomes for SKYLIGHT 1 and SKYLIGHT 2 in the FAS [7, 9-11]

	SKYLIGHT 1		SKYLIGHT 2	
	Fezolinetant 45 mg (n= 174)	Placebo (n= 175)	Fezolinetant 45 mg (n= 167)	Placebo (n= 167)
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	
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.				

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 .[11] The longer term data from week 24 and week 52 have been used in the economic base case.

*Other data were also assessed but remain confidential**

2.3. Health-related Quality of Life outcomes

In DAYLIGHT, health related quality of life (HRQoL) 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.[12]

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.[7]

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 a relevant comparator.[8-10] 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.[8] 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 45mg 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.[9, 10]

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; the MHRA recommends that 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, 7, 13]

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 may 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.[7, 8]

- 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.[7, 9, 10]
- The submitting company provided additional evidence to support the positioning from a pooled subpopulation of participants deemed unsuitable for HRT from the SKYLIGHT 1 and SKYLIGHT 2 studies. The reduction in frequency of VMS in the fezolinetant group compared with placebo was consistent with the full population from baseline to 4 and 12 weeks. Results from the fezolinetant group during the active extension period indicated that the reduction in VMS was sustained at 24 and 52 weeks.[11]

4.2. Key uncertainties

- The submitting company considered that no active treatment was the only relevant comparator in the population deemed unsuitable for HRT; the placebo group in the studies has been used as a proxy for no active treatment.[5] Although alternative non-hormonal treatments are available, clinical experts indicated that efficacy can be variable and side effects often limit tolerability. The company has provided no direct or indirect evidence for fezolinetant versus alternative non-hormonal treatments within this submission and therefore comparative efficacy is 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.[7-10, 14]
- 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.[8-10]
- 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, 6, 15]

*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.[13]

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. 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 years.
Population	Fezolinetant was considered in a cohort of menopausal women with moderate to severe VMS for whom HRT is deemed unsuitable.
Comparators	No active treatment. This consisted of healthcare resource costs only and no medicine acquisition costs were included.
Model description	A Markov model with six health states was used. Four health states were defined based on average daily moderate to severe VMS frequency, with health states of 0 ≤ VMS frequency < 2, 2 ≤ VMS frequency < 7, 7 ≤ VMS frequency < 9, and VMS frequency ≥ 9. The remaining two health states captured natural VMS cessation and death. A four-week cycle length was used.

Clinical data	DAYLIGHT was the source of the baseline VMS frequency health state distribution, fezolinetant efficacy up to week 24, placebo efficacy data (for no active treatment) up to week 12, and discontinuation rates up to week 24 in both arms.[8] The pooled analysis of SKYLIGHT 1 and 2 (HRT-unsuitable population) was used as the source of fezolinetant efficacy data for weeks 24 to 52 and the discontinuation rate beyond week 24.[11] The company was unable to source relevant published evidence on the natural history of VMS, which was instead gathered from a structured expert elicitation (SEE) exercise (using six experts) to obtain judgements on the natural history of postmenopausal women who were not currently receiving any treatment for VMS and were deemed HRT-unsuitable. The natural history data were obtained by asking experts to estimate the proportion experiencing different daily VMS frequencies across three timepoints (year 1, 3 and 6) so that an overall trajectory could be mapped out. The base case used the year 6 proportions only from the SEE, as this was viewed to be the most realistic reflection of natural progression with VMS. The rate of VMS cessation was sourced from literature.[16] Mortality rates were assumed to be the same for the general female population in Scotland.[17]
Extrapolation	Upon entering the model, patients were distributed across the VMS frequency health states according to the DAYLIGHT baseline distribution and received either fezolinetant or no active treatment. In the fezolinetant arm, whilst on treatment, patients transitioned between the VMS frequency health states according to transition probabilities derived from observed fezolinetant data in DAYLIGHT up to week 24 and the pooled SKYLIGHT 1 and 2 (HRT-unsuitable population) for weeks 24 to 52. After week 52, transition probabilities were estimated based on the average from weeks 24 to 52. Upon fezolinetant discontinuation, patients were considered off-treatment and transitioned between VMS health states according to transition probabilities derived from the natural history of VMS. All natural history transition probabilities were based on the year 6 estimates of natural history from the SEE exercise, assuming a linear change from baseline, with a waning effect applied from year 6 onwards. In the no active treatment arm, patients transitioned between the VMS frequency health states according to transition probabilities derived from placebo arm data in DAYLIGHT up to week 12. At week 12, the placebo effect was removed for all no active treatment arm patients, and they subsequently transitioned between VMS health states according to transition probabilities derived from the natural history of VMS. Discontinuation could also occur before week 12, informed by placebo arm discontinuation rates from DAYLIGHT. Patients could also transition to the VMS cessation health state, discontinuing treatment (if still receiving treatment) and remaining in this health state until death. All patients were at risk of death at any time and could transition to the death state.
Quality of life	The utility values were obtained from EQ-5D-5L data collected in DAYLIGHT. The submitting company noted concerns over the EQ-5D instrument's ability to capture the health impacts associated with menopause, and adjusted utility values based on feedback from its clinical experts. These adjustments reduced the $7 \leq$ VMS frequency < 9 and VMS frequency ≥ 9 health state utility values by 5% and set the $0 \leq$ VMS frequency < 2 utility value to 0.810. The clinician-adjusted utility values used in the model were 0.843 (VMS cessation), 0.810 ($0 \leq$ VMS frequency < 2), 0.793 ($2 \leq$ VMS frequency < 7), 0.746 ($7 \leq$ VMS frequency < 9), and 0.710 (VMS frequency ≥ 9).

Costs and resource use	Fezolinetant medicine acquisition costs and VMS frequency health state costs were included in the model.
PAS	There is no PAS in place for fezolinetant.

6.2. Results

The base case results are summarised in Table 6.2.

Table 6.2: Base case results

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
fezolinetant	2,836	6.66	-	-	-
no active treatment	1,674	6.54	1,163	0.12	10,063

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

6.3. Sensitivity analyses

The scenario analysis is summarised in Table 6.3. ICERs were sensitive to the natural history distribution, utility values, and the placebo effect.

Table 6.3: Scenario analysis results

	Parameter	Base case	Scenario	Incr. cost	Incr. QALY	ICER (£/QALY)
-	Base case	-	-	1,163	0.12	10,063
1a	Time horizon	10 years	3 years	626	0.09	6,629
1b			20 years	1,245	0.12	10,806
2	Baseline patient distribution	DAYLIGHT	SEE estimated 'year 0'	1,491	0.05	27,753
3a	Placebo effect (no active treatment)	Week 0–12: DAYLIGHT 0–12 per cycle	Natural history	1,109	0.13	8,811
3b			No transitions	1,108	0.13	8,773
3c			Week 0 to 24: Week 0–12 DAYLIGHT and Week 12 – 24 DAYLIGHT	1,208	0.11	11,327
4a	Natural history application	Only use Year 6 distribution	Use year 1 distribution at year 2	1,367	0.08	17,671
4b			Only use year 3 and year 6 distributions	1,334	0.08	16,055
4c			Use year 1, year 3, and year 6 distributions directly from SEE.	1,473	0.06	25,946
5	Natural history waning	Applied post year 6	Not applied	1,159	0.12	9,948
6	Distribution following discontinuation	Natural history / SEE exercise	DAYLIGHT Baseline	1,167	0.11	10,181

7	Post-discontinuation transitions	Natural history transitions	No transitions	539	0.235	2,292
8a	Utility values	Clinical expert adjusted DAYLIGHT estimates	DAYLIGHT	1,163	0.08	13,776
8b			Clinician adjusted Pooled SKYLIGHT 1 & 2 (HRT-unsuitable)	1,163	0.12	9,549
8c			Pooled SKYLIGHT 1 & 2 (HRT-unsuitable)	1,163	0.06	18,144
9	Liver function testing	Liver function test costs only	Liver function test costs and additional physician visits for testing	1,267	0.12	10,965
C1 (1a, 6, 7)	Removal of SEE natural history. Time horizon of 3 years. Reset to baseline distribution (DAYLIGHT) post discontinuation. No transitions post discontinuation.			496	0.12	4,153
C2 (3c, 4c, 8a)	Placebo effect of 24 weeks. Natural history applies Year 1, Year 3, and Year 6 from SEE. DAYLIGHT utility values.			1,506	0.05	31,906

Abbreviations: C = combined scenario; ICER = incremental cost-effectiveness ratio; Incr = incremental; HRT = hormone replacement therapy; QALY = quality-adjusted life years; SEE = structured expert elicitation; VMS = vasomotor symptoms.

6.4. Key strengths

- The company performed an economic systematic literature review to identify relevant literature on previous economic evaluations, utility values and healthcare resource use.
- Appropriate sources were used to value resource use and medicine acquisition costs.

6.5. Key uncertainties

- There were uncertainties in the natural history transitions derived from the SEE exercise, leading to uncertainty in the efficacy of no active treatment and the comparative efficacy of fezolinetant. Firstly, given the challenges of estimating the course of VMS, there was notable variation present in the estimated proportions experiencing different daily VMS frequencies across the three timepoints (year 1, 3 and 6) from the six experts. The observed variation in the estimates, as seen in the standard errors and 95% credible intervals, could not be accounted for in isolated scenarios or one-way deterministic sensitivity analysis. Secondly, when the SEE exercise natural history estimates were applied to the DAYLIGHT baseline distribution, this resulted in a rapid rate of VMS frequency decline, which was viewed as unrealistically fast for the resolution of VMS by company clinical experts. This was likely due to the SEE exercise not being anchored to the baseline VMS frequency distribution of DAYLIGHT. Given this, the base case only used the year 6 proportions from the SEE exercise, but multiple alternatives were available as scenario analyses which used different timepoints (Scenarios 4a, 4b and 4c). An additional scenario was provided that estimated a baseline VMS frequency distribution from the SEE exercise,

rather than DAYLIGHT (Scenario 2). Thirdly, no dedicated systematic literature review was performed to identify studies on the natural history of VMS. Finally, given the uncertainties with the SEE exercise, the submitting company presented a combined scenario that removed natural history transitions from the model and reset patients to the DAYLIGHT VMS frequency baseline distribution upon discontinuation (Combined Scenario 1). However, this should be seen cautiously, as it retains no active treatment patients in the higher VMS frequency health states and with treatment effects preserved in the fezolinetant arm.

- There was uncertainty regarding the placebo effect in the model and the resulting comparative efficacy for fezolinetant. In the no active treatment arm, the submitting company considered the use of 12 weeks of DAYLIGHT placebo data to be conservative, as practice would not include placebo treatment and additional GP contact. Alternative scenarios of natural history, no transitions, and applying 24 weeks of placebo arm data from DAYLIGHT were available (Scenarios 3a, 3b, and 3c). However, no scenario was considered that extended the placebo effect beyond 24 weeks as DAYLIGHT was only placebo controlled to 24 weeks, and extrapolation was viewed as inappropriate by the submitting company. In the fezolinetant arm, absolute treatment effects were used post week 12 rather than relative treatment effects, meaning no adjustment for the placebo effect was made in this arm. A scenario using relative treatment effects for fezolinetant was requested but not provided. The submitting company viewed that this would present modelling challenges and applying relative treatment effects to natural history would lead to a loss of granularity in the modelling of fezolinetant efficacy compared with using the observed trial data.
- There was uncertainty in the adjustment to utility values derived from DAYLIGHT, with a basic adjustment applied based on company clinical expert assumptions. A scenario removed this adjustment (Scenario 8a). In addition, both clinician-adjusted and unadjusted utility values from the pooled SKYLIGHT 1 and 2 (HRT-unsuitable population) studies were applied in scenario analyses (Scenarios 8b and 8c). However, these should be seen with caution as they were only derived from 12 weeks of double-blind data. Nonetheless, these scenarios highlighted sensitivity in economic results from the utility values.
- There was uncertainty in whether no active treatment was the only relevant comparator for fezolinetant. Whilst this was supported by some SMC clinical experts, others highlighted a range of treatment options, including SSRIs, SNRIs, clonidine, gabapentin and pregabalin. However, the SMC clinical experts noted that the benefits of these treatments are short lived or that they are not well tolerated. Whilst the responses indicated that no active treatment is likely to be the main comparator, there are potentially a series of minor comparators omitted from this economic analysis.
- The long-term efficacy of fezolinetant was uncertain, as the transition probabilities were derived from comparative efficacy data available only up to 24 weeks in the DAYLIGHT study. Beyond this point, transition probabilities were based on uncontrolled pooled data from SKYLIGHT 1 and 2 (HRT-unsuitable population) for weeks 24 to 52, with transition probabilities past 52 weeks extrapolated from this. To potentially reduce uncertainty in

longer-term efficacy projections, a shortened time horizon of 3 years was considered (Scenario 1a).

- There were uncertainties in the categorisation and use of VMS frequency health states. Firstly, the thresholds were partly derived from EQ-5D utility data, but the utility values between health states did not always show statistically significant differences. In addition, the EQ-5D may be capturing other quality of life aspects of menopause rather than just VMS. SMC clinical experts generally viewed the thresholds as reasonable. Secondly, the submitting company considered VMS frequency as a proxy for VMS severity. Whilst some SMC clinical experts viewed this as reasonable, one expert highlighted that it was relevant to consider the impact of less frequent but more severe VMS. SMC clinical experts also highlighted sleep disturbance would be considered when assessing severity, which may not be captured in these health states.
- The costs associated with liver function tests may be underestimated. Although the analysis included the costs of liver function tests for patients receiving fezolinetant at baseline, and cycles 1, 2, and 3, no additional healthcare resource use costs were allocated. The submitting company provided a scenario to reflect the increase in resource use due to liver function tests (Scenario 9). In addition, costs associated with subsequent periodic liver function tests were not included, but the cost impact of these would be minor.

7. Conclusion

After considering all the available evidence, the Committee was unable to accept fezolinetant for 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 September 2024.[5]

9. Additional Information

9.1 Product availability date

14 December 2023

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 04 April 2025.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 68,947 patients eligible for treatment with fezolinetant in year 1 and 71,155 in year 5, to which confidential uptake rates were applied. The estimated uptake rate is uncertain based on SMC clinical experts' opinion and may be overestimated in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues.

*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 16 May 2025.

**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 is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme 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. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards 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.