NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using fezolinetant in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: March 2025

Note that this document is not NICE's final guidance on fezolinetant. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using fezolinetant in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 28 April 2025
- Second evaluation committee meeting: To be confirmed.
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Fezolinetant should not be used to treat moderate to severe vasomotor symptoms caused by menopause.

1.1 This recommendation is not intended to affect treatment with fezolinetant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Fezolinetant is not required to be funded in the NHS in England to treat moderate to severe vasomotor symptoms caused by menopause. It should not be used routinely in the NHS in England.

This is because there is not enough evidence to determine whether fezolinetant is value for money.

Why the committee made these recommendations

Usual treatment for vasomotor symptoms (hot flushes and night sweats) is hormone replacement therapy. For this evaluation, the company asked for fezolinetant to be considered only for vasomotor symptoms caused by menopause when hormone replacement therapy is unsuitable. This does not include everyone who it is licensed for.

Clinical trial evidence shows that fezolinetant decreases the frequency and severity of moderate to severe vasomotor symptoms compared with placebo. But there are uncertainties about the clinical evidence. This is because the people in the trials do not reflect everyone who would be eligible to have fezolinetant in the NHS. There is

also no robust evidence to show how moderate to severe vasomotor symptoms change over time.

There are also uncertainties in the economic model because it does not adequately reflect:

- vasomotor symptoms that are important to those experiencing symptoms
- the impact of treatment on the severity of these symptoms
- everyone who would be eligible for fezolinetant in the NHS.

Because of these uncertainties, it is not possible to use the model to reliably estimate whether fezolinetant is better than other treatment options. Because of the uncertainties in the clinical and economic evidence it is not possible to determine the most likely cost-effectiveness estimates for fezolinetant. So, it should not be used.

2 Information about fezolinetant

Marketing authorisation indication

2.1 Fezolinetant (Veoza, Astellas Pharma) is indicated for 'the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for fezolinetant.

Price

2.3 The list price for fezolinetant is £44.80 per 28-tablet pack.

2.4 Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The evaluation committee considered evidence submitted by Astellas Pharma, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Menopause and vasomotor symptoms

3.1 Menopause is a natural part of ageing when menstruation stops because of lower hormone levels, usually defined by a person not having a period for 12 consecutive months. It usually happens between 45 and 55 years. But it can happen earlier because of surgery to remove the ovaries or uterus, treatment for cancer or an inherited condition. Symptoms vary from person to person but vasomotor symptoms, more commonly known as hot flushes and night sweats, are the most common symptoms. Vasomotor symptoms can also include heat in the face and upper body, red or flushed face, rapid heartbeat, sweating, chills and anxiety. Severity of vasomotor symptoms can be graded mild to severe. Patient experts told the committee that they started experiencing vasomotor symptoms during perimenopause (the beginning of menopause when people experience symptoms of having lower hormone levels, but periods have not fully stopped). These vasomotor symptoms were severe and disruptive, leading to anxiety and trouble sleeping. The symptoms got worse and more disruptive over years, having a significant impact on quality of life. Patient experts shared their experiences of seeking healthcare for vasomotor symptoms, stating that they felt misunderstood and dismissed when first visiting a GP. They said healthcare professionals needed better education and understanding of vasomotor symptoms and the impact they have on individuals. One expert reported being sent away because they still had periods, and instead seeking advice and support from friends. The committee acknowledged the severity of the condition and the substantial impact it has on people's quality of life. It concluded

there is a need for effective treatments to manage vasomotor symptoms caused by menopause, both in perimenopause and menopause.

Clinical management

Treatment pathway

3.2 Experts explained that the treatment pathway for treating vasomotor symptoms is well defined. NICE's guideline on menopause identification and management (NG23) states that hormone replacement therapy (HRT) is the primary treatment option for vasomotor symptoms caused by menopause. It suggests that menopause-specific cognitive behavioural therapy (CBT) could be offered in addition to HRT or when HRT is unsuitable. HRT is contraindicated in people with breast or oestrogen-dependant cancers, and NICE guideline 101 on the diagnosis and management of early and locally advanced breast cancer recommends stopping HRT in women who are diagnosed with breast cancer. Non-hormonal treatments such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may be used when HRT is unsuitable. But NG23 states these should not be routinely offered as a first-line treatment for vasomotor symptoms alone. NG101 recommends SSRIs for people with breast cancer for relieving menopause symptoms, particularly hot flushes, but not for people taking tamoxifen. The committee concluded that HRT is the first treatment people would be offered for managing menopause symptoms, including vasomotor symptoms. Non-hormonal treatments may be used when HRT is unsuitable. The committee noted there are limited treatment options available to treat vasomotor symptoms when HRT is unsuitable, and there is a particular unmet need for people with breast or oestrogen-dependant cancers.

Population for whom HRT is unsuitable

3.3 The company proposed fezolinetant for use when HRT is unsuitable, which is narrower than its marketing authorisation. The company suggested that the population would include the following groups:

- 'HRT-contraindicated': people for whom HRT is contraindicated
- 'HRT-caution': people for whom a medical risk assessment of a specific caution has concluded that the risk of HRT outweighs the benefit, for example in people with diabetes or heart disease
- 'HRT-stopper': people who have previously taken HRT but can no longer take HRT
- 'HRT-averse': people for whom HRT is indicated but do not wish to take HRT.

A clinical expert at the meeting advised that the population for whom HRT would be unsuitable was likely to be small. This was because HRT is the gold standard for treatment of the broad range of symptoms caused by menopause including vasomotor symptoms. They said that with increased awareness and understanding of HRT's benefits and risks, and the availability of both oral and transdermal formulations of HRT, most people with moderate to severe vasomotor symptoms would be having HRT. The number of people in the HRT-caution and HRT-averse groups would be low in current practice. The clinical expert also noted that the main group of patients for whom HRT would be unsuitable are those who have or have had breast cancer or other oestrogen-dependent cancers. Fezolinetant is also not recommended for people who have breast cancer or other oestrogen-dependent cancers, and an individual risk assessment is advised for people who have had breast cancer or other oestrogen-dependent cancers because there is no clinical trial data to determine its safety of clinical effectiveness in these groups. The committee agreed there is a particular unmet need for people with breast cancer or other oestrogen-dependant cancers who are experiencing vasomotor symptoms caused by menopause but acknowledged that fezolinetant would not be used in

this group. The committee concluded that it would consider fezolinetant for people with moderate to severe vasomotor symptoms associated with the menopause, for whom HRT is unsuitable.

Monitoring requirements and implications for prescribing setting

3.4 The company has positioned fezolinetant to be prescribed in primary care. The committee noted that fezolinetant is not recommended for people with liver disease. After reported observations of rare liver injury with fezolinetant by the Food and Drugs Administration, extra liver blood tests has been added to its MHRA marketing authorisation. This was added after the company submission and EAG report. Liver monitoring is needed before treatment, monthly for the first 3 months after treatment, then periodically based on clinician discretion. Liver blood tests must also be done when there are symptoms suggestive of liver damage. The committee noted uncertainty about the follow-up testing after 3 months. It heard from clinical experts that although they were not concerned from a clinical perspective about manageable liver risks, managing the liver monitoring within primary care would have a large impact in terms of appointments and incur additional costs (see section 3.13). A clinical expert submission suggested that because of the need for additional liver monitoring, fezolinetant should be prescribed in secondary care or by a GP with special interest. The committee decided that primary care may not be appropriate because of the need for liver monitoring, and that GPs would prefer to use SSRIs or other established non-hormonal treatments because they are already widely used in primary care and do not have additional liver monitoring requirements. The committee concluded that offering fezolinetant in secondary care may be more appropriate.

Relevant comparators

3.5 The company proposed that when HRT is unsuitable, ‘no pharmacological treatment’ is the relevant comparator. It stated that expert opinion indicated that CBT and other psychological therapies are typically used as add-on therapies and are not comparators in NHS clinical practice. The

company also stated the other non-hormonal pharmacological treatments were not appropriate comparators because NG23 does not recommend their use. Its clinical experts had noted limited efficacy and unpleasant side effects from non-hormonal treatments such as SSRIs and SNRIs.

The EAG agreed that positioning fezolinetant when HRT was unsuitable was reasonable and therefore HRT was not a relevant comparator. It also agreed with excluding non-pharmacological comparators such as CBT because clinical opinion noted they are rarely prescribed in NHS practice. But the EAG did not agree with the exclusion of non-hormonal treatments such as SSRIs as comparators, stating that lower efficacy is not a suitable reason for exclusion. It also stated that NG23 recommendations on the use of these treatments were based on the first-line superiority of HRT, and do not say that they should not be used when HRT is unsuitable. Also, clinical advice to the EAG suggested that non-hormonal treatments are prescribed to about 1 in 5 people with vasomotor symptoms in NHS practice. Clinical experts and patient experts at the meeting also confirmed that these treatments can be offered.

The committee concluded that non-pharmacological treatments and HRT were not relevant comparators. However, it noted that non-hormonal treatments are offered in primary care and should therefore be included as a relevant comparator for fezolinetant if it is offered in primary care. If fezolinetant were offered in secondary care (see section 3.4) it may be an option at a later point in the treatment pathway, after HRT and non-hormonal treatments. At this point, 'no pharmacological treatment' may be the relevant comparator.

Clinical effectiveness

Clinical trials

3.6 Clinical evidence for fezolinetant came from 3 clinical trials: DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2. DAYLIGHT was a phase 3, randomised,

multicentre trial that compared fezolinetant with placebo for a follow-up period of 24 weeks. SKYLIGHT 1 and 2 were phase 2 randomised multicentre trials with identical designs. They compared fezolinetant with placebo for 12 weeks, plus an uncontrolled 40-week extension period. Participants in all 3 trials were aged 40 to 65 with moderate to severe vasomotor symptoms. DAYLIGHT only included participants if HRT was deemed unsuitable, but SKYLIGHT 1 and 2 included a pre-defined subgroup of people for whom HRT was unsuitable. In all the trials, participants were experiencing a minimum average of 7 moderate to severe vasomotor symptom events each day at baseline. All the trials reported mean change in vasomotor symptom frequency and severity from baseline to the end of follow up. Overall, DAYLIGHT and the pooled SKYLIGHT 1 and 2 data showed statistically significant reductions in both vasomotor symptom frequency and severity. But the EAG stated that these outcomes were subject to high risk of bias because in the analysis missing outcome data was assumed to be 'missing at random' and missing data was assumed to be similar to the treatment group mean for that outcome. The EAG considered this approach unsuitable and overoptimistic in favour of fezolinetant because missing data is likely to be because of treatment-related discontinuation because of loss of efficacy or treatment side effects. This may mean that the treatment effect of fezolinetant is lower in the group of people with missing data compared with the trial population. The EAG stated that a more conservative approach would be more appropriate. The EAG suggested that the alternative outcomes of the proportion of responders with more than 50%, more than 75% and 100% reduction in daily vasomotor symptom frequency had less risk of bias because of a more conservative approach to handling missing data. There was a higher proportion of responders across each category (more than 50%, more than 75% and 100% response) in the fezolinetant group compared with placebo. The committee concluded that fezolinetant was clinically effective compared with placebo in reducing daily vasomotor symptom frequency and severity

in the trial population, but there was uncertainty about the size of the benefit because of the methods the company used to handle missing data.

Generalisability to the NHS population

3.7 The clinical trials had narrower populations than the marketing authorisation for fezolinetant or for people who would be expected to have fezolinetant in the NHS. DAYLIGHT and SKYLIGHT 1 and 2 did not recruit people with perimenopause, chronic diseases, elevated blood pressure, or fewer than 7 moderate to severe daily vasomotor symptom events per day. Patient experts explained that it was the severe effect of vasomotor symptoms rather than number of events that had the biggest impact. The committee was concerned that the trial did not reflect clinical practice, because some people with fewer than 7 vasomotor symptom events per day but whose vasomotor symptoms were still moderate to severe would be eligible for and want treatment. The EAG commented that in a SKYLIGHT 1 and 2 subgroup analysis that grouped participants by baseline daily vasomotor symptom frequency, improvements with fezolinetant appeared to be driven by the subgroup experiencing higher frequencies of vasomotor symptoms (10 or more events each day). This subgroup showed a greater benefit of fezolinetant compared with placebo than other subgroups experiencing fewer daily vasomotor symptoms. Subgroup data based on baseline vasomotor symptom frequency had not been presented for DAYLIGHT. The EAG noted that this meant the trials may overestimate the benefit of fezolinetant because they included people who had a larger number of daily vasomotor symptoms who may be expected to have a larger benefit; people with fewer vasomotor symptoms, who may have fezolinetant in clinical practice, may expect a smaller benefit. The company stated that its marketing authorisation covers vasomotor symptoms associated with menopause and this includes vasomotor symptoms during perimenopause and postmenopause. The trial only included postmenopausal people.

The company stated that it was reasonable to expect that there would be similar safety and efficacy outcomes for perimenopausal and postmenopausal people because published studies show that the physiological mechanisms for vasomotor symptoms are consistent from perimenopause to postmenopause. Clinical advice to the EAG agreed that this assumption was reasonable. But it also noted there was a higher proportion of people with hysterectomies in the SKYLIGHT trials, that early menopause induced by hysterectomy is associated with more severe vasomotor symptoms, and treatment response may differ between this group and the wider population. The committee agreed that the trial populations differed from the NHS population that would have fezolinetant. So, the trial results may not be fully generalisable to the population eligible for fezolinetant, particularly those with severe but less frequent vasomotor symptoms. The committee was concerned by the exclusion of people with fewer than 7 vasomotor symptoms per day because they would be included in the NHS population, and it had not been demonstrated that fezolinetant is clinically effective in these people. So, it concluded that the trial populations were not generalisable to the NHS population and the effectiveness in this population remained uncertain.

Indirect treatment comparison

3.8 The company did not include indirect treatment comparisons in its submission, because it stated that 'no alternative treatment' was the most appropriate comparator. It did include an 'exploratory' network meta-analysis (NMA) in its clarification response to the EAG, which compared fezolinetant with non-hormonal treatment comparators. The analysis only included evidence for fezolinetant (the key trials described in section 3.6) and one SSRI (paroxetine). Two trials compared paroxetine with placebo. The company excluded trials for other non-hormonal treatments because they were drugs or doses not used in clinical practice. The results showed that fezolinetant was more effective than paroxetine for change in moderate to severe vasomotor symptom frequency. The EAG was unable

to validate the NMA because of the company's limited reporting of the analysis. The EAG noted that it could not apply the results to the model because the model does not allow for relative treatment effects to be used (see section 3.11). It also identified an additional published NMA (Morga 2023) that was sponsored by the company. The published NMA showed little evidence that fezolinetant improved moderate to severe vasomotor symptom frequency over SSRIs, SNRIs and gabapentin. But the EAG noted that the NMA had several limitations, including high risk of bias from missing data. The committee noted that the NMA provided by the company did not include the range of non-hormonal treatments that may be used in NHS practice. The committee concluded that it would prefer to see NMA evidence for all treatments used in the NHS when available, with an assessment of limitations and uncertainty around the data. Relative effects from the NMA should then inform the modelled cost-effectiveness estimates for fezolinetant compared with non-hormonal treatments.

Adverse events

3.9 In its submission, the company reported that treatment-related adverse events were similar for fezolinetant and placebo in all the trials. The committee noted the extra stipulations for liver monitoring, which has been introduced since fezolinetant was licensed for use in the UK (see section 3.4). The EAG noted that the European Medicines Agency had reported a higher number of neoplasms in SKYLIGHT 4 (a 52-week safety study comparing fezolinetant with placebo), but had assessed this difference to be likely due to chance. The EAG identified additional published analyses of the fezolinetant trial data (Douxfils 2023), which suggested an increased incidence of neoplasms in the fezolinetant arm. The company stated that the FDA concluded that 50% of malignancy events for fezolinetant were likely caused by preexisting malignancy. It also stated that malignant neoplasms were only observed in SKYLIGHT 4, and that analysis of the phase 2 and 3 trials suggests that treatment-related neoplasms were unlikely. The company also stated that the statistical

pooling methods (Peto odds ratio) in Douxfils 2023 were inappropriate for rare events. The committee noted the discussion of neoplasms in the clinical literature but accepted the conclusion of the drug regulatory agencies that neoplasms were not treatment related.

Cost effectiveness

Company's modelling approach

3.10 The company provided a Markov cohort model that included 4 health states defined by vasomotor symptom frequency. The model compared fezolinetant with no treatment in a cohort of people who had 7 or more daily vasomotor symptoms at baseline and were followed over a 10-year time horizon using 4-weekly model cycles. Because vasomotor symptoms will naturally stop over time, natural cessation was modelled using an assumption that the median duration of experiencing vasomotor symptoms is 7.4 years. The health states based on vasomotor symptom frequency were defined by a range of daily frequencies. The cut-offs for the ranges were determined based on the DAYLIGHT baseline (a cut off of 7 or more daily vasomotor symptoms) and statistical analyses (generalised estimating equation models) of utility values associated with different frequency thresholds. These utility values were derived from EQ-5D-5L collected in DAYLIGHT.

The company's justification for basing health states on vasomotor symptom frequency alone was that frequency was a primary endpoint in the trials and more objective than severity, and that frequency and severity are correlated. The EAG stated that using a structure based solely on frequency does not capture the impact on severity. Clinical advice to the EAG was that using frequency as a proxy for severity was a concern and not usual NHS practice. The EAG noted that vasomotor symptom severity was a key primary outcome in SKYLIGHT 1 and 2 and a key secondary outcome DAYLIGHT. The EAG considered that the data presented by the company for correlation between vasomotor symptom

severity and frequency only showed moderate to weak correlation. The EAG also had concerns that the methods used to determine frequency thresholds for the health states included using utility values to define health states. This is because EQ-5D is also likely to capture quality of life for menopause symptoms other than vasomotor symptoms (see section 3.12). Also, the differences between each health state's estimated utility values were small with overlapping confidence intervals. The committee noted that by not incorporating severity, which was a separate outcome in the trials, the current model may not be capturing all the benefits of fezolinetant. The committee noted the patient experts' experiences that frequency was less of a consideration than the severe impact of symptoms (see section 3.7). It concluded that the model structure does not adequately capture health states relevant to people with moderate to severe vasomotor symptoms and that it was inappropriate for decision making.

Data from trials and estimates of natural history

3.11 Transition probabilities for the fezolinetant arm were calculated based on DAYLIGHT data up to week 24, and then pooled SKYLIGHT 1 and 2 data up to week 52, which was then extrapolated beyond 52 weeks (while on treatment). Transition probabilities for the placebo arm were calculated based on placebo data from DAYLIGHT up to week 12. The model applied absolute changes to vasomotor symptom frequency rather than relative treatment effects. The EAG also noted that in the 'no active treatment arm', the placebo effect is no longer applied from week 12. When people in the model stop treatment, they follow the natural history of moderate to severe vasomotor symptoms until symptoms stop, death, or the end of the model time horizon. The company did not identify published evidence on the natural history, so it generated natural history estimates using structured expert elicitation. It asked 6 clinical experts to estimate what proportion of people with untreated vasomotor symptoms would be experiencing different vasomotor symptom frequencies over time (after 1, 3, and 6 years). The structured expert elicitation exercise did

not state that people would have 7 or more vasomotor symptoms at baseline and the experts were asked to consider a postmenopausal population. The company reported high uncertainty in the estimates, due in part to a dramatic and implausible shift to lower vasomotor symptom frequencies between the DAYLIGHT baseline and year 1 natural history estimates. To address this, the company further adjusted the estimates based on the opinion of 1 additional expert. After further consultation with experts, the company decided to only use the year 6 natural history estimates and assumed a linear change from baseline to year 6 in the model. The EAG noted that a systematic review to specifically identify natural history studies was not done and, when requested at clarification, the company said it would be unlikely to resolve uncertainties about the natural history estimates. The EAG advised that the expert elicitation was not anchored to the baseline distribution of vasomotor symptom frequency from DAYLIGHT, which may be why the baseline distribution and natural history estimates were not compatible. The committee expressed disappointment in the reported lack of robust natural history data for a condition that affects a large number of people. The committee decided the outputs of the structured expert elicitation were not fit for purpose because the baseline distribution of vasomotor symptom frequency from DAYLIGHT was not defined to the experts and the elicited distributions lack face validity. The committee also decided that a model structure that did not allow comparison of relative treatment effects and limited trial data to 12 weeks in the 'no treatment' arm was highly problematic. The impact of these modelling choices was that after 12 weeks, the placebo arm reverts to very high frequencies of symptomatic vasomotor events. The committee decided that it was not possible to use the model to estimate reliable estimates of any benefits of fezolinetant compared with no treatment (or any other comparator). It concluded that the misalignment between the baseline number of events, natural history estimates and approach to placebo adjustment were all linked and needed to be addressed in a coherent way.

Health state utilities

3.12 Utility values for the model were derived from EQ-5D-5L data from DAYLIGHT, mapped to EQ-5D-3L. These were used to define the vasomotor symptom frequency health states and utility values for each state using generalised estimating equation models (see section 3.10). The company made subsequent adjustments to decrease the utility values for some of the vasomotor symptom frequency health states, informed by clinical opinion. The company explained that these adjustments were made because of the insensitivity of EQ-5D to measure symptom improvements in menopause, and these adjustments were further validated by patient experts who felt the estimates to be conservative. The EAG was unable to assess the appropriateness of the final model because of the limited detail on how the final values were estimated. But it advised that adjusting utilities based on the input of 1 clinical expert is highly uncertain. It also noted that the utility values for the placebo group from DAYLIGHT were higher than in the fezolinetant group, but in SKYLIGHT 1 and 2 the utilities for the placebo group were lower than the utilities for the fezolinetant group. The EAG's scenarios exploring different utility values increased the incremental cost-effectiveness ratios. The EAG also noted that because EQ-5D is a generic measure of health, it may be capturing wider symptoms of menopause in addition to vasomotor symptoms. The committee stated that altering EQ-5D values based on input from a single clinical expert was inappropriate. The committee acknowledged that EQ-5D is NICE's preferred measure for health-related quality of life (see NICE's health technology evaluations manual), but there are some circumstances when EQ-5D may not be the most appropriate measure. The committee suggested it may be useful to explore health-related quality of life for vasomotor symptoms using a disease-specific tool, such as the Menopause-Specific Quality of Life measure, to estimate the utility values. The committee acknowledged there was no UK value set for the Menopause-Specific Quality of Life

measure but determined that using a disease-specific tool with a non-UK value set was an appropriate alternative approach to explore.

Uncaptured costs

3.13 The committee considered the potential additional costs and consequences that were not captured in the model. This included costs for additional liver monitoring and liver blood testing, and any subsequent costs in cases of treatment-related liver damage. The modelled costs assumed that fezolinetant would be primarily prescribed in primary care. The committee also noted that it may be more suitable for fezolinetant to be prescribed in secondary care (see section 3.4), which may also incur different costs. The committee concluded that the modelled costs should include liver blood tests and appointments for liver monitoring. The modelled costs should also reflect the setting in which fezolinetant is prescribed and monitored (primary or secondary care).

Cost-effectiveness estimates

Acceptable ICER

3.14 The committee concluded that it was unable to determine a plausible cost-effectiveness estimate for the whole population with moderate to severe vasomotor symptoms for whom HRT is unsuitable. This is because:

- the setting in which fezolinetant would be prescribed is unclear. The company assumes fezolinetant would be prescribed in primary care. The costs and other implications (for example on population, or comparators) of secondary care prescribing need to be explored (see section 3.4 and section 3.13)
- not all relevant comparators have been included in the company's base case. If fezolinetant is prescribed in primary care, non-hormonal treatments should be included as relevant comparators (see section 3.5 and 3.8)
- there is a lack of clinical effectiveness data for some people with moderate to severe vasomotor symptoms for whom HRT is unsuitable.

Clinical evidence for fezolinetant was only available for people with 7 or more daily vasomotor symptom events, so the effectiveness in the wider population is unknown (see section 3.7)

- the model structure and health states do not adequately capture the impact on patients of having moderate to severe vasomotor symptoms, or the treatments effects on these, because health states are based on the frequency of daily symptoms and do not model changes in severity (see section 3.10)
- the model did not allow for a comparison of relative treatment effects between modelled treatment arms and compared absolute treatment effects over different time periods in each modelled treatment arm (see section 3.11)
- the natural history estimates were based on clinical opinion, were highly uncertain, were estimated without defining the baseline distribution of vasomotor symptom frequency and lacked face validity (see section 3.11).
- the approach of adjusting utility values based on clinical opinion was inappropriate. There may be reasons why utility values based on EQ-5D do not capture vasomotor symptom specific utility, but further exploration of other approaches is needed (see section 3.12)
- there are uncaptured costs, including the costs for additional liver monitoring (see section 3.13).

Other factors

Equality

3.15 The committee considered several equality considerations that were raised during scoping, in the company and expert submissions, and in NG23. It acknowledged that the unmet need for treatment and lack of historical evidence in the menopausal population reflects the historical lack of research into women's health. The committee expressed disappointment that there is still a lack of research and innovation in this

area, particularly when it covers a large population. It noted that younger people can be affected by premature or induced menopause, including abrupt onset of vasomotor symptoms. Vasomotor symptoms are also more prevalent, with greater severity and duration in certain ethnicities including Black and Hispanic people. Also, Black African and Caribbean people may be less likely to choose HRT. The committee also noted that access to appropriate care is a potential issue for trans and non-binary people. The lack of treatment options for people with breast cancer or oestrogen-dependant cancers, which can be disabling conditions, was raised as a potential equality consideration. There may also be a greater impact and prevalence of vasomotor symptoms based on people's type of work and educational level. The committee acknowledged all these considerations and concluded it is important to consider them as this appraisal progresses.

Conclusion

Recommendation

3.16 The committee concluded that both the clinical evidence and economic modelling were highly uncertain and did not represent the NHS population who would be eligible for fezolinetant. So, they are unsuitable for decision making. The committee would need to see updated analyses that better reflect the NHS vasomotor symptom population and natural history of the disease (see section 3.14). It decided there were no plausible cost-effectiveness estimates. So, it concluded that fezolinetant should not be used to treat moderate to severe vasomotor symptoms caused by menopause.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the fezolinetant being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Lauren Elston

Technical lead

Mary Hughes

Technical adviser

Louise Jafferally

Project manager

Ross Dent

Associate director

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