NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause

1 Recommendation

1.1 Fezolinetant can be used as an option to treat moderate to severe vasomotor symptoms caused by menopause when hormone replacement therapy is unsuitable

1.2 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 clinician consider it appropriate to stop.

What this means in practice

Fezolinetant must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Fezolinetant must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that fezolinetant provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made this recommendation

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 suggests that fezolinetant decreases the frequency and severity of moderate to severe vasomotor symptoms compared with placebo. Fezolinetant has not been directly compared with non-hormonal treatments. Indirect comparisons suggest that it may have similar effectiveness to non-hormonal treatments, but this is uncertain.

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, fezolinetant can 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.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Astellas Pharma will be included here when guidance is published.

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 to 55 years. But it can happen earlier because of surgery to remove the ovaries, 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. They can 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. The European Medicines Agency and the US Food and Drug Agency (FDA) define moderate vasomotor symptoms as a sensation of heat with sweating, with the individual able to continue usual activity. Severe vasomotor symptoms are defined as a sensation of heat with sweating, with the individual not able to continue usual activity. The 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. The symptoms got worse and more disruptive over years, having a significant impact on quality of life. The 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 need better education and understanding of vasomotor symptoms and the impact they have on people. One patient expert reported being sent away because they still had periods, and instead seeking advice and support from friends. The responses to the draft guidance discussed symptoms associated with vasomotor symptoms such as lack of sleep, brain fog, fatigue and depression. They also discussed the impact of these on people's ability to work or exercise, relationships, and the increased risk of cardiovascular disease with unmanaged vasomotor symptoms. 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 in perimenopause and menopause.

Clinical management

Treatment pathway

3.2 The clinical experts explained that the treatment pathway for treating vasomotor symptoms is well defined. NICE's guideline on identification and management of menopause (NG23) states that hormone replacement therapy (HRT) is the primary treatment option for vasomotor symptoms caused by menopause. HRT is contraindicated in people with breast or oestrogen-dependant cancers. NICE's guideline on early and locally advanced breast cancer (NG1010) recommends stopping HRT in women who are diagnosed with breast cancer. NG23 suggests that menopause-specific cognitive behavioural therapy (CBT) could be offered in addition to HRT or when HRT is unsuitable. But responses to the draft guidance consultation and advice from the patient and clinical experts explained that CBT does not reduce physical symptoms for many people. It is also difficult to access, with long waiting lists for treatment. Non-hormonal treatments such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are sometimes used when HRT is unsuitable. But NG23 states these should not be routinely

offered as a first-line treatment for vasomotor symptoms alone. But NG101 does recommend considering SSRIs for people with breast cancer for relieving menopause symptoms, particularly hot flushes, but some SSRIs are not recommended for people taking tamoxifen. Treatment decisions are unique and are taken in line with patient preference. The clinical expert stated that fezolinetant, as a different option for some people, was a 'game changing' treatment for people who could access it. 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 condition has concluded that the risk of HRT outweighs the benefit, for example in people with diabetes or heart disease
- 'HRT-stopper': people who have had HRT but can no longer have it
- 'HRT-averse': people who do not want to have HRT.

A clinical expert at the meeting advised that the population for whom HRT would be unsuitable is likely to be small. This is 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 oral and transdermal HRT formulations, most

people with moderate to severe vasomotor symptoms would have HRT. The number of people in the HRT-caution and HRT-averse groups would be low in current practice. The committee acknowledged that this number may rise if fezolinetant was made available because some people may choose fezolinetant over HRT. The clinical expert noted that the main group for whom HRT would be unsuitable are people who have or have had breast cancer or other oestrogen-dependent cancers. Fezolinetant is not recommended for people who have breast cancer or other oestrogen-dependent cancers. For people who have had breast cancer or other oestrogen-dependent cancers and are no longer on any cancer treatments, an individual risk assessment is advised. This is because there is no clinical trial data to determine fezolinetant's safety or 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 it 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 when HRT is unsuitable.

Liver 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 US FDA, extra liver blood tests have been added to its Medicines and Healthcare products Regulatory Agency marketing authorisation. Liver monitoring is needed before treatment, monthly for the first 3 months after starting treatment, then periodically based on clinician discretion. Liver blood tests must also be done when there are symptoms suggesting liver damage. The committee noted uncertainty about the follow-up testing after 3 months. The clinical experts explained that, from a clinical perspective, they considered liver risks to be manageable. But

they added that managing liver monitoring in primary care would have a large impact in terms of appointments and incur additional costs. 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 noted that primary care may not be appropriate for people with more complex conditions and liver monitoring is not possible. GPs might 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. Some people would be referred to secondary care, and offered fezolinetant in secondary care.

At the second committee meeting, the committee acknowledged the comments made in the consultation responses, and by patient and clinical experts, that prescribing fezolinetant only in a secondary care setting would introduce regional and socioeconomic disparities. This is because waiting times for secondary care would impede access to fezolinetant. The company provided results from the GP omnibus survey that indicated most GPs would be confident in making clinical decisions based on liver test results. But, the responses on which settings fezolinetant should be prescribed in were mixed:

- 38% said primary care only
- 23% said secondary care only and
- 38% said both settings

The omnibus survey results also reported that for the majority of people for whom HRT was unsuitable, a large proportion would have SSRIs, SNRIs or no treatment. The clinical expert stated that liver function tests are easy to access and interpret and that any liver injury would be reversible. The clinical expert thought that one plausible outcome was that most prescribing would be done in primary care. But for some more complex cases, potentially including people with a risk of liver damage, prescribing might be in secondary care. The committee acknowledged

that some cases may need to be prescribed in secondary care or with specialist help from secondary care. The committee noted that an 'advice and guidance' approach could be taken in primary care to have support from secondary care in some cases. The committee concluded that fezolinetant could be prescribed:

- in primary care
- in primary care with 'advice and guidance' from secondary care, and
- in secondary care.

The EAG noted that the model only included primary care costs. So, the committee concluded that to properly assess the cost effectiveness of fezolinetant it would have to consider the additional cost of fezolinetant in primary care with a proportion of cases being prescribed with support from secondary care. The company submitted analysis modelling 30% of the population being prescribed in primary care but incurring a cost of £20 for additional advice and guidance from secondary care. The committee concluded that this analysis likely reflected how fezolinetant might be used in practice and that it was appropriate for decision making.

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. There are also a range of non-hormonal treatments that may be used, often off-label, to treat vasomotor symptoms. These include:

- SSRIs such as:
  - citalopram
  - sertraline
  - fluoxetine and
  - paroxetine, and
- SNRIs such as

  - desvenflaxine and
  - venlafaxine, and
- anti-convulsants such as gabapentin.

The company's clinical experts had noted limited efficacy and unpleasant side effects from non-hormonal treatments.

The EAG agreed that positioning fezolinetant when HRT was unsuitable was reasonable and so HRT was not a relevant comparator. It also agreed with excluding non-pharmacological comparators such as CBT because clinical opinion noted these 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 said that the recommendations in NG23 on using these treatments were based on the first-line superiority of HRT. NG23 does not say that they should not be used when HRT is unsuitable. Also, clinical advice to the EAG suggested that non-hormonal treatments such as SSRIs are prescribed for about 1 in 5 people with vasomotor symptoms in NHS practice. The clinical and patient experts confirmed that SSRI's and SNRI's can be offered. The committee concluded that non-pharmacological treatments and HRT were not relevant comparators. But it noted that non-hormonal treatments are offered in primary care and so should be included as a relevant comparator for fezolinetant. If fezolinetant were offered in secondary care 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.

In the second meeting the clinical expert restated that while SSRIs are not always their preferred treatment, they are used in clinical practice. The committee noted that fezolinetant is likely to be available for prescription in both primary and secondary care settings. It also noted that people who can have fezolinetant would currently be having either

no active treatment or non-hormonal treatments. So, it concluded that both no active treatment and non-hormonal treatments are relevant comparators. The committee decided that a blended comparator approach would be appropriate to determine the cost effectiveness of fezolinetant. The company provided updated analyses that modelled a blend of no active treatment and desvenflaxine as comparators using proportions from Glynne et al. 2025 modelled 41.5% having no active treatment and 58.5% having desvenlafaxine. A scenario was also provided that used the results of the company submitted GP omnibus survey. It modelled 31.1% no active treatment and 68.9% desvenflaxine. The committee noted that of the non-hormonal comparators, only comparisons with desvenflaxine and paroxetine were available. It concluded that desvenflaxine was a reasonable proxy for non-hormonal treatments for this evaluation. The committee concluded that the most appropriate comparators are likely to be non-hormonal treatments in primary care and no treatment in secondary care. It concluded that the comparator weighted using the proportions from Glynne et al. was appropriate for decision making.

Clinical effectiveness

Clinical trials

3.6 Clinical evidence for fezolinetant came from the DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 clinical trials. 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. People in all 3 trials were aged 40 to 65 years with moderate to severe vasomotor symptoms. DAYLIGHT only included people if HRT was unsuitable, and SKYLIGHT 1 and 2 included a pre-defined subgroup of people for whom HRT was unsuitable. In all the trials, people 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. This was because missing outcome data was assumed to be 'missing at random' and was assumed to be similar to the treatment group mean for that outcome. The EAG advised that this approach is unsuitable and overoptimistic in favour of fezolinetant. This is because missing data is likely to be a result of people stopping treatment when it stops working or causes side effects. So, the treatment effect of fezolinetant may be 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. It 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 it added that 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. The 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. This was because some people with fewer than 7 vasomotor symptom events per day but whose vasomotor symptoms were still moderate to severe would be suitable for and want treatment. The EAG commented on a SKYLIGHT 1 and 2 subgroup analysis that grouped people by baseline daily vasomotor symptom frequency. It noted that improvements with fezolinetant could be affected 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. This was 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, including during perimenopause and post menopause. The trial only included people post menopause. The EAG stated that people during perimenopause may have lower frequencies of vasomotor symptoms. This further indicates that the trial results may overestimate the benefits of fezolinetant compared with what might be seen in clinical practice.

The company noted that published studies show that the physiological mechanisms for vasomotor symptoms are consistent from perimenopause to post menopause. So it stated that it was reasonable to expect that there would be similar safety and efficacy outcomes for people during perimenopause and post menopause. Clinical advice to the EAG agreed that this assumption was reasonable. But the EAG also noted:

- there was a higher proportion of people with hysterectomies in the SKYLIGHT trials
- early menopause induced by hysterectomy is associated with more severe vasomotor symptoms, and
- treatment response may differ between people with hysterectomies 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 suitable 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. These people would be included in the NHS population, but it had not been demonstrated that fezolinetant is clinically effective for these people. So, it concluded that the trial populations were not fully generalisable to the NHS population and the effectiveness in this population remained uncertain.

In the second meeting, the committee reiterated its concerns about generalisability. But it acknowledged that the criterion of 7 vasomotor symptoms or more was mandated by the US FDA in the clinical trial. The committee concluded that the effect size seen in the clinical trial might not reflect clinical practice. It added that the effect of people with chronic diseases or high blood pressure not being represented in the clinical trial would also affect the generalisability of the evidence. It concluded that the cost-effectiveness estimates are uncertain.

Indirect treatment comparison

3.8 After the first committee meeting, the company provided indirect treatment comparisons with a network meta-analyses (NMAs) of non-hormonal pharmacological treatments. There was no data available for many non-hormonal treatments. But, the company did a simple NMA for fezolinetant compared with 1 (restricted) dose of desvenlafaxine. The NMA analysed

reductions of 75% or more in vasomotor symptoms and discontinuation rates. There was also a comparison with paroxetine for discontinuation rates only. In this comparison, responses rates were not compared because response was defined as 50% or greater in the source studies (not 75%). The company did restricted dose (1 dose) and extended dose (all doses) NMAs. The EAG stated that an extended dose NMA would more reliably estimate between-study heterogeneity by including additional evidence in the network, which reduced uncertainty. The EAG recommended using random-effect NMAs for both outcomes instead of the company's approach of using random effects for response and fixed effects for discontinuation rates. In the consultation response, missing data was imputed using last observation carried forward (LOCF). The EAG acknowledged that the company had to adopt this approach because all the comparator trials reported results based on LOCF. In the economic model, the NMA odds ratio for fezolinetant compared with desvenlafaxine, based on LOCF imputation, was applied to fezolinetant response rates derived using a more conservative imputation method. This assumed missing data for the response outcome represented non-responders. This mixing of methods introduced a potential inconsistency. But the EAG advised it was a reasonable assumption given the constraints with the data (see section 3.6). The committee noted that, independent of the preferred assumptions, the confidence intervals of relative effectiveness of fezolinetant compared with desvenlafaxine included the possibility of there being no treatment effect (company base case 0.84, 95% credible interval [CrI] 0.36 to 2.09; EAG base case 0.84, 95% CrI 0.42 to 1.73). It felt that this suggested the benefit of fezolinetant is not as great as expected by the clinical expert (see section 3.2). The clinical expert agreed that the benefit was lower than would be expected and that there was no clear explanation as to why greater benefit was not observed. But the committee acknowledged that SSRIs are used in this indication off-label. NICE's manual states that when considering 'off-label', 'unlicensed' or 'unregulated' comparator technologies, the committee will take into account the extent and quality of evidence, particularly for safety

and efficacy, for the unregulated use. The EAG noted that the evidence for SSRIs was not high quality and had a particular limitation of missing data. This might bias some of the studies in favour of the SSRIs. The committee decided it was possible that limitations of the studies for desvenflaxine might bias the indirect treatment comparison and the estimates of cost effectiveness against fezolinetant. But, this was very uncertain. It explained that it would take this into account in its decision making. The committee concluded that the EAGs choice of parameters and methods for NMA was its preferred approach.

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 stipulation 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 et al. 2023), which suggested an increased incidence of neoplasms in the fezolinetant arm. The company stated that the US 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 et al. 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. The cohort 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 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 in DAYLIGHT. The EAG stated 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. 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. 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.

Company's updated modelling approach

3.11 After the first committee meeting the company developed a new response-based model structure to compare fezolinetant with no active treatment, desenlafaxine and paroxetine. The health states were defined by response in terms of a reduction in vasomotor symptoms frequency from baseline. After 12 weeks of treatment, people who have a 75% or more reduction in vasomotor symptoms move to the 'responder' state. In the no active treatment arm the remainder moved to the off-treatment state. In the active treatment arm, the company assumed that half of the remainder would have a 50% to 74% reduction in vasomotor symptoms and could be considered partial responders. The EAG agreed that the new model structure addresses the core issues raised at the first committee meeting, including that it:

- includes relative treatment effects, removing the issue around using absolute effects discussed in the first meeting
- removes vasomotor symptom frequency health states and the need to define a baseline for these states
- uses trial data instead of natural history
- accounts for placebo effect in both arms.

The EAG stated that while the new model structure addresses core issues, it introduces misalignment with utilities and health states. This is because the 'no active treatment' arm has 5 health states and the 'active treatment' arm has 6 health states, to include partial responders (50% or more to less than 75%). The committee concluded that the

model resolved most of the concerns raised at the first committee but introduces a misalignment that might impact the cost-effectiveness results.

Model structure mismatch

3.12 In the new model structure, the active treatment groups included an extra state compared with the no active treatment group. This creates a misalignment with the utility values used for the health states. The utility values for the no active treatment arm were based on a weighted average of responders (who had a 75% or more reduction) and non-responders (who did not have a 75% or more reduction). This resulted in a structure that differs from the active treatment arm, which had 3 categories of response (response, partial response and no response) and a lower response threshold of above 50% for the responders (where 50% to 75% reduction in symptoms were considered partial responders and over 75% considered responders). The company stated that partial response data was not available for the non-hormonal treatments but would be available for the no active treatment arm from the pooled SKYLIGHT and DAYLIGHT data. The company's partial responder state included a 1-year stopping rule at which point all partial responders stopped treatment.

The EAG suggested removing misalignment by defining a response as having a 50% reduction in vasomotor symptoms for all comparators including no active treatment. The EAG's clinical advisers did not support the use of the 1-year stopping rule and said it would not reflect real practice. The patient experts agreed that if a drug was working, even a partial response is better that nothing and they would be likely to want to continue the treatment. The committee concluded that the stopping rule should not be included for partial responders. The committee acknowledged there would be partial responders in the active treatment arm but there would also be people in the no active treatment arm who had a 50% to 74% reduction in vasomotor symptoms frequency, which should be modelled. The committee concluded that both active and no

active treatment arms should include the same health states and a partial response should be modelled for both. The company updated the model to include a partial response health state in both model arms. It used the pooled clinical trial data for the placebo arm to determine partial response for the no active treatment arm. It retained the assumption the proportion of individuals who achieved a partial response for fezolinetant should be used to estimate partial response for other active treatments. The committee concluded that this analysis resolved its concerns around model misalignment and that it would use this updated model for its decision making.

Health state utilities

3.13 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. 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. The adjustments were further validated by the patient experts who felt the estimates to be conservative. The EAG was unable to assess the appropriateness of the utilities used in 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 (ICERs). The EAG 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 decided that altering EQ-5D values based on

input from 1 clinical expert was inappropriate. It acknowledged that EQ-5D is NICE's preferred measure for health-related quality of life (see NICE's technology appraisal and highly specialised technologies guidance 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 to estimate the utility values, such as the Menopause-Specific Quality of Life measure. The committee acknowledged there was no UK value set for the Menopause-Specific Quality of Life measure. But it determined that using a disease-specific tool with a non-UK value set was an appropriate alternative approach to explore.

Updated health state utilities

3.14 After the first meeting, the company acknowledged the committee's preferences and removed the adjustment of the EQ-5D values. In the updated model the company used the mean of the fezolinetant and no active treatment arms, weighted by responder status in the absence of reported utility values for non-hormonal treatments. The EAG raised the concern that this effectively means that the company is applying treatment-dependent utility values for responders and non-responders. This is despite people in the response state all reaching the same level of reduction in vasomotor symptoms. The EAG said this lacks validity. Its clinical adviser stated that the utility values should be independent of the treatment received if people have met the same response criterion. The company explained that the model only included adverse events up to 3 weeks, and there may be additional adverse events for the non-hormonal comparators that are not modelled. It felt this justified having lower utilities in the non-hormonal treatment arm. The committee had not seen any strong evidence to support this and decided that the company had not made a strong case for treatment-specific utility values. These might be justified if the treatments cause significant non-overlapping adverse events, or the health-related quality of life is strongly correlated

with time on treatment. In the absence of evidence supporting the longer-term impacts on quality of life for non-hormonal comparators relative to fezolinetant, the committee's preference was to apply treatment-independent utilities for active treatments. Responses from the draft guidance consultation also noted there may be a benefit from fezolinetant of reducing vasomotor symptoms severity that might not be fully captured by the EQ-5D. Instead, it may only be captured by modelling the effect of fezolinetant on vasomotor symptoms frequency. The company submitted updated modelling that modelled the same utility values per health state for fezolinetant and desvenflaxine (using the pooled trial values for fezolinetant) and slightly lower values for no active treatment (using the pooled trial values for placebo). The committee thought that it was acceptable to model different utility values for no active treatment compared with active treatments. This was because it reflected the clinical trial results and because there might be some effect on symptom severity of active treatment.

Costs of liver function tests

3.15 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, with associated blood tests, and any subsequent costs in cases of treatment-related liver damage. 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). In the updated model after draft guidance consultation, the company included liver testing costs. The EAG noted that the additional nursing costs associated with liver monitoring had not been included, and included these costs in its own base case. At the second meeting, the committee

concluded that the additional nursing costs should be included in the analysis.

Cost-effectiveness estimates

Committee's preferred assumptions

3.16 The committee concluded that the company's updated model structure, which includes a partial response health state in all arms, was acceptable for decision making. Its modelling preferences were to:

- use the company's updated model with equivalent health states in all arms (see section 3.11)
- assume that 30% of prescribing will be done in primary care but with support from secondary care with appropriate costs applied (see section 3.4)
- use a blended comparator consisting of 41.5% no active treatment and 58.5% non-hormonal treatments (see section 3.5)
- use the simple, extended dose random effects NMA for both response and discontinuation analyses for the comparison with desvenflaxine (see section 3.8)
- not apply a stopping rule to partial responders (see section 3.12)
- model liver testing costs and associated nurse time (see section 3.15).

Acceptable ICER

3.17 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjust life year gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted uncertainties about generalisability of the clinical trial evidence to NHS practice and acknowledged the potential for:

- limitations of the evidence for non-hormonal treatments to bias the model against fezolinetant (see section 3.8)
- the uncertainty in the NMA design and the limited evidence of the benefit of fezolinetant from the results of the NMA (see section 3.8)
- the uncertainty in the derivation of the utility values (see section 3.14)
- fezolinetant to address health inequalities and health equality issues (see section 3.18)
- uncaptured benefits of fezolinetant because of issues with the EQ-5D and the lack of explicit modelling of symptom severity (see section 3.19).

Acknowledging these uncertainties and the potential uncaptured benefits, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources.

Other factors

Equality

3.18 The committee considered equality considerations 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 Black 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-dependent cancers

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. During the draft consultation, responses from professional organisations explained that the current system favours those who can afford to pay for private care including CBT or fezolinetant. So, not recommending this treatment may increase health inequalities. They also noted the consistent underrepresentation of some groups in research in this area, for example there is no high quality data for people from ethnic minority backgrounds. Online responses to the draft guidance consultation noted that cancer is a protected characteristic because it is classed as a disability under the equalities act, and that choosing not to use HRT may be based on religion. The committee acknowledged all these considerations and concluded it would take them into account in its decision making.

Uncaptured benefits

3.19 The draft consultation responses reinforced the committee's concerns that a model based on reduction in vasomotor symptoms frequency would not capture the impact of a reduction in severity of vasomotor symptoms. The committee also acknowledged that EQ-5D may not be sensitive enough to reflect the whole treatment effect anticipated when considering reductions in vasomotor symptoms. It concluded it would take these into account in its decision making.

Conclusion

Recommendation

3.20 The committee took into account of its preferred assumptions, key uncertainties in the evidence and other factors in its decision making. It concluded the ICERs are within the range that NICE normally considers an acceptable use of NHS resources. So, fezolinetant can be used.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has moderate to severe vasomotor symptoms and the healthcare professional responsible for their care thinks that fezolinetant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

Chairs

Stephen O'Brien and James Fotheringham

Chairs, 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 and Alice Bell

Technical leads

Mary Hughes and Samuel Slayen

Technical advisers

Louise Jafferally and Leena Issa

Project managers

Ross Dent and Lorna Dunning

Associate directors

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