**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Fezolinetant for treating vasomotor symptoms associated with the menopause (ID5071)

**Response to stakeholder organisation comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comment 1: the draft remit and proposed process

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| Appropriateness of an evaluation and proposed evaluation route | Astellas Pharma Ltd | Yes, this is an appropriate topic to refer to NICE for Single Technology Appraisal. | Thank you |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | Could consider multiple technology appraisal as we have an evidence base for CBT as a non-pharmacological menopause symptom control option. CBT has been researched in women with breast cancer and shown to help with reduction of vasomotor symptoms. Clinicians will be critically considering Fezolinetant as a treatment option in breast cancer patients. | Thank you. CBT is being appraised in the partial update to the clinical guideline (NG23). It has been included in the draft guideline so has been added to the scope as a possible comparator. |
| | British Menopause Society (BMS) | Thank you, this is appropriate (MD)<br>OK (JB) | Thank you |

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| | | This is an appropriate evaluation for an intervention that can have an important role in clinical practice for women who can't take or who do not wish to take HRT.(HH) | |
| Wording | Astellas Pharma Ltd | Yes, the remit broadly reflects the clinical and cost effectiveness of fezolinetant for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause. | Thank you |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | Yes | Thank you |
| | British Menopause Society (BMS) | Yes (MD)<br><br>It may be worth including the short comings of the listed non-hormonal treatments in terms of effectiveness, side effects and lack of license (HC)<br><br>Timing: I would say soon. There are a lot of desperate breast cancer patients waiting for this drug. Some may resort to HRT via private clinics while waiting. (JB)<br><br>Yes. Clinical efficacy and cost-effectiveness are relevant questions. (HH) | Thank you.<br><br>The background section is intended to be a brief summary. However, the fact that some of these treatments are used outside of the terms of their marketing authorisation has been added. |
| Timing issues | Astellas Pharma Ltd | Fezolinetant is a first-in-class non-hormonal therapy that has demonstrated statistically and clinically significant reductions in the frequency and severity of VMS and improvements to quality of life through the DAYLIGHT, SKYLIGHT 1 and 2 randomised, placebo-controlled trials. Fezolinetant addresses a critical unmet need for safe and effective treatment options for | Thank you |

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| | | women with severe to moderate VMS associated with menopause for whom HRT is unsuitable. Fezolinetant is licenced and available on the UK market. | |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | Would be good to have the results within 6 months – perhaps too ambitious. | Thank you. The topic has been scheduled into the work programme. The timing for an appraisal is usually aligned as closely to the marketing authorisation as possible. In this appraisal, the company requested delays in order to facilitate a suitably comprehensive and robust submission. |
| | British Menopause Society (BMS) | Routine (MD)<br><br>Many women struggle to access effective non-hormonal treatments and so there is an urgent need for this evaluation (HC) | Thank you |
| Additional comments | United Kingdom Clinical Pharmacy Association (UKCPA) | Considering cost benefits, please note that a non-hormonal prescribed treatment option for menopause vasomotor symptom control is critically needed in clinical practice for those patients who cannot be or choose not to take HRT. It would be helpful if the assessment for cost benefit provides specific directive for those patients who cannot be advised to take HRT, due | Thank you, comments noted, the scope includes the use of fezolinetant for people in whom HRT is considered suitable, and for people in whom |

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| | | to HRT risks outweighing benefit. Also please highlight if there is a need for research to help answer this point. | HRT is not considered suitable. |

**Comment 2: the draft scope**

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| Background information | Astellas Pharma Ltd | This section appropriately reflects that this appraisal relates specifically to the treatment of VMS and not the treatment of menopause symptoms more broadly. As such, it is much improved on the previous draft scope and Astellas have only one further comment.<br><br>There is one paragraph introduced into this draft which Astellas considers factually inaccurate: the final paragraph states "*When HRT is not suitable, treatments for VMS include SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), clonidine, and anti-convulsants such as gabapentin and pregabalin*". Pharmacological treatments represent a broadly applicable relevant comparator in this appraisal, but NICE NG23 clearly states "*Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone*." This statement reflects the lack of robust phase 3 trial evidence for these treatments in moderate-to-severe VMS, which are not licensed for VMS. Astellas acknowledge that NICE NG101 does suggest SSRI antidepressants may be a comparator in women with breast cancer. This does not apply to HRT-unsuitable women without breast cancer, for whom no treatment is the only first line comparator.<br><br>Astellas' position on comparators has been validated with 3 UK clinical experts, who agreed that no treatment was the most relevant comparator for | Thank you. Clinical experts at the scoping workshop and during the scope consultation highlighted that SSRIs, SNRIs and clonidine are all used in clinical practice when HRT is not suitable. Therefore, these have been retained in the scope. Whilst we acknowledge the current NICE guideline recommendations, this sentence in the scope reflects the feedback we have had from stakeholders on what is currently used in the NHS. |

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| | | this appraisal and noted issues relating to lack of effectiveness, and to developing dependence with a number of the options mentioned by NICE. | |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | Background:<br>- Consider including perimenopause phase descriptor.<br>- In line 'Vasomotor symptoms have been linked to [delete depression] [substitute with low moods and anxiety that occur with menopause]<br><br>References:<br>Please include full publication paper refs not abstracts. | Thank you, this section has been amended. |
| | British Menopause Society (BMS) | The text of the Background section could perhaps be re-ordered:<br>*Hormone replacement therapy (HRT) is the main treatment option for vasomotor*<br>*symptoms in menopause. NICE recommends:*<br>*• oestrogen and progestogen for those with a uterus; or oestrogen alone for those without a uterus (NG23).*<br><br>*When HRT is not suitable, treatments for VMS include SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), clonidine, and anti-convulsants such as*<br>*gabapentin and pregabalin.*<br>*NICE recommends:*<br>*• selective serotonin reuptake inhibitor (SSRI) antidepressants for those with breast cancer, but not for those taking tamoxifen (NG101).*<br>*NG101 also notes that HRT should be stopped if breast cancer is diagnosed and*<br>*should not be offered routinely when there is a history of breast cancer unless in* | Thank you, the order of the background section has been amended. |

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| | | *exceptional circumstances.* (MD)<br><br>Not enough emphasis is placed on the severity of symptoms for some women, and the impact that these can have on many aspects of life. In addition, the need for effective, safe non-hormonal treatment is not just for patients who have had breast cancer, but also for other hormone dependant cancers, people who have had significant side effects from HRT, some medical conditions and those with a personal choice to avoid hormonal treatment. (HC)<br><br>Some SSRIs can be used with tamoxifen eg citalopram and escitalopram. (JB)<br><br>Fine (HH) | |
| Population | Astellas Pharma Ltd | The population defined in the draft scope is appropriate. | Thank you |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | Yes, as per Fezolinetant's clinical trials run by manufacturer. | Thank you |
| | British Menopause Society (BMS) | Yes (MD)<br>Yes (HC)<br>OK (JB)<br>Yes (HH) | Thank you |

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| Subgroups | Astellas Pharma Ltd | It is not anticipated that subgroup efficacy analyses will be relevant in this appraisal. | Thank you for your comment. |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | If there is an evidence base, consider 2 sub-groups that come to mind - breast cancer patients [cannot take HRT] and UK ethnic minority patients, especially Black African / Caribbean [choose not to take HRT]. | People for whom HRT is considered unsuitable will be considered separately (see comparators section of the scope). This includes people who cannot have HRT and those who chose not to have HRT. The point that UK ethnic minority patients may chose not to take HRT is noted in the Equalities Impact Assessment and can be considered by the committee. |
| | British Menopause Society (BMS) | Patients with breast cancer and other hormonally sensitive cancers. I appreciate trials not completed in this group of patients but we need guidance on this as they may be the main group that will benefit from this drug. (JB)<br><br>Assessing response in women with contraindication to taking hormonal treatment (e.g. breast cancer patients) compared to other interventions. (HH) | People for whom HRT is considered unsuitable will be considered separately (see comparators section of the scope). |

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| | | Assessing response in women who do not have a contraindication to taking hormonal treatment compared but who wish to avoid taking HRT. (HH) | |
| Comparators | Astellas Pharma Ltd | Comparators are defined by HRT suitability; Astellas agree with this approach.<br>**HRT-suitable:**<br>• Astellas agree that women who are suitable for HRT should have it, and do not propose to submit any comparison for women who are HRT-suitable.<br>**HRT-unsuitable:**<br>• Astellas agree that no pharmacological treatment is a relevant comparator and consider it to be the only relevant comparator for fezolinetant.<br>• Astellas do not agree that non-hormonal pharmacological treatments represent a relevant comparator in this appraisal, as NICE NG23 clearly states “Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone.” This statement reflects the lack of robust phase 3 trial evidence for these treatments in moderate-to-severe VMS, which are not licensed for VMS. Astellas acknowledge that NICE NG101 does suggest SSRI antidepressants may be a comparator in women with breast cancer. This does not apply to HRT-unsuitable women without breast cancer, for whom no treatment is the only comparator. Astellas’ position on comparators has been validated with 3 UK clinical experts, who agreed that no treatment was the most relevant comparator for this appraisal and noted issues relating to lack of effectiveness, and to developing dependence with a number of the options mentioned by | Thank you for your comment. Clinical experts at the scoping workshop and during the scope consultation highlighted that SSRIs, SNRIs and clonidine are all used in clinical practice when HRT is not suitable. Therefore, these have been retained in the scope. Whilst we acknowledge the current NICE guideline recommendations, this sentence in the scope reflects the feedback we have had from stakeholders on what is currently used in the NHS. |

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| | | NICE. | |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | Intervention Table:<br>Comparator: Non-Pharmacological treatment – CBT | Thank you<br><br>CBT is being appraised in the partial update to the clinical guideline (NG23). It has been included in the draft guideline so has been added to the scope as a possible comparator. |
| | British Menopause Society (BMS) | Oxybutynin should be a comparator; there is evidence of efficacy in treatment of vasomotor symptoms and it was identified by NIHR as the topic of a commissioned call. The HTA-funded BLUSH study (multicentre RCT of non-hormonal therapies) is ready to recruit but currently paused because of oxybutynin supply problems. (MD)<br><br>Since CBT is being recommended and has been found to be effective, I wonder if this should be included as a comparator, though in reality it can be used alongside pharmacological treatments.<br>Oxybutinin could also be considered as a comparator. (HC)<br><br>Need to include oxybutynin (JB)<br><br>Yes | Thank you<br>Oxybutynin has not been included as it is currently under investigation and does not appear to be used in routine UK clinical practice.<br><br>CBT is being appraised in the partial update to the clinical guideline (NG23). It has been included in the draft |

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| | | Comparators:<br>HRT<br>Non hormonal SSRI / SNRI<br>Gabapentin / pregabalin<br>Oxybutynin<br>Also comparison to non medical interventions such as CBT. (HH) | guideline so has been added to the scope as a possible comparator. |
| Outcomes | Astellas Pharma Ltd | The outcome measures presented broadly capture the most important health-related benefits of fezolinetant. | Thank you |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | See subgroups comments above | Thank you |
| | British Menopause Society (BMS) | Acceptability of treatment, and treatment continuation, need to be considered in comparisons with existing therapies.<br>In clinical practice, many patients unable to take HRT do not tolerate the alternative agents such as SSRI/gabapentin. (MD)<br><br>Yes (HC)<br><br>Need to include the potential side-effects of the current non-hormonal prescribed options.<br>(JB)<br>Yes (HH) | Thank you. Potential side-effects would be captured in the outcome 'adverse effects of treatment'. Treatment discontinuation is implicitly considered within the economic analysis. |

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| Equality | Astellas Pharma Ltd | There is a substantial unmet need for treatment options for women with VMS associated with menopause, and historically there has been a lack of innovation in this area of women's health, particularly for non-hormonal treatment options. New non-hormonal treatment options would therefore be welcome to this patient group.<br><br>There are also differences in the prevalence and severity of VMS between ethnicities which should be considered. VMS have been reported as more prevalent in black and Hispanic women than other ethnicities. [1, 2] Differences in VMS severity between socioeconomic levels also exist. [3] Women in a household where the main earner works in semi-skilled or unskilled manual work have been reported to be more likely to have difficulty with physical and psychological symptoms than those where the main earner works in a managerial role. [3]<br><br>Additionally, the NICE clinical guideline relevant to this appraisal (NG23), which is currently being updated, should be aligned to the anticipated recommendations in the technology appraisal for fezolinetant in this indication. This is critical to ensure consistent provision of treatment in UK clinical practice; Astellas have been advised by UK clinical experts that NICE guidelines are heavily relied upon by NHS prescribers and a positive recommendation within the TA is not sufficient to ensure equality of access.<br><br>Astellas also notes the questions for consultation relating to the setting of fezolinetant prescription in either primary or secondary care. Fezolinetant is anticipated to be prescribed primarily in primary care by GPs; feedback to Astellas from UK HCPs is that access to specialist menopause clinics is extremely location-dependent with some areas lacking clinics entirely (the Southwest of England), and some areas facing waiting lists of up to a year (such as in the Southeast of England). Such disparities in access would be exacerbated should fezolinetant not be available for prescription in a primary care setting. Indeed, the availability of fezolinetant in primary care may | Thank you. These considerations are included in the Equalities Impact Assessment and any potential impact to the guidance will be discussed by committee. |

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| | | alleviate some of the pressure on specialist menopause clinics by providing an effective treatment for women who currently lack any treatment options. | |
| | United Kingdom Clinical Pharmacy Association (UKCPA) | If there is an evidence base, consider assessing UK ethnic minority patients, (eg Black African / Caribbean) who often choose not to take HRT. | Thank you. This has been included in the Equalities Impact Assessment and any potential impact to the guidance will be discussed by committee. |
| | British Menopause Society (BMS) | Fine (HH) | Thank you |
| Other considerations | Astellas Pharma Ltd | None | Thank you |
| | British Menopause Society (BMS) | As above after application quality standards to assess uptake / discontinuation compared to other interventions and research recommendations to assess cost-effectiveness compared to other interventions.(HH) | Thank you |
| Questions for consultation | Astellas Pharma Ltd | **Where do you consider fezolinetant will fit into the existing treatment pathway for menopause? What are the main treatments used in clinical practice for people for whom HRT is not considered suitable?**<br>Fezolinetant is anticipated to be positioned for use in women who are considered unsuitable for HRT. | Thank you for your comments.<br>Clinical experts at the scoping workshop highlighted that SSRIs, SNRIs and clonidine |

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| | | According to the current NICE clinical guideline on the menopause (NG23), SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine are not routinely recommended as first-line treatment for VMS alone. This is primarily due to the limited efficacy of SSRIs and SNRIs in relieving VMS, as well as the high rates of discontinuation resulting from unpleasant adverse effects. Additionally, the evidence for the efficacy of clonidine in VMS is limited and conflicting. [4]<br><br>Astellas has been advised by UK clinical experts that the variable efficacy, safety profile and non-specific mechanism of action of SSRIs and SNRIs in targeting VMS make them less favourable as alternative treatment options compared with fezolinetant for HRT-unsuitable women. As such, fezolinetant would be expected to be considered ahead of SSRIs and SNRIs in the treatment pathway for these women, specifically as first-line treatment for HRT-caution, HRT-contraindicated, and HRT-averse; and second-line for HRT stoppers. It is important to note that Astellas recognises that for many women being treated for menopausal symptoms who are HRT-eligible, HRT remains the first-line treatment for moderate to severe VMS. However, for HRT-unsuitable women (i.e., HRT-caution, HRT-contraindicated, HRT-stoppers, and HRT-averse), fezolinetant would be the treatment of choice.<br><br>Therefore, for women categorised as HRT-caution, HRT-contraindicated, HRT-stoppers, or HRT-averse, no active treatment represents the sole relevant comparator to fezolinetant in the existing treatment pathway.<br><br>**Please select from the following, will fezolinetant be:**<br>**A. Prescribed in primary care with routine follow-up in primary care**<br>**B. Prescribed in secondary care with routine follow-up in primary care**<br>**C. Prescribed in secondary care with routine follow-up in secondary care**<br>**D. Other (please give details):** | are all used in clinical practice when HRT is not suitable. Therefore, these have been retained in the scope. Whilst we acknowledge the current NICE guideline recommendations, this sentence in the scope reflects the feedback we have had from stakeholders on what is currently used in the NHS.<br><br>The setting in which fezolinetant is expected to be used and the discussion of potential substantial health-related benefits unlikely to be included in the QALY calculation will be discussed by committee.<br><br>Equalities considerations have been added to the |

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| | | Astellas' position on the anticipated setting for prescribing fezolinetant has been validated with 3 UK clinical experts, who all agreed that it is anticipated that the majority of women will follow option A above; a small number of women may be referred to specialists due to the complexity of their symptoms and therefore follow B or C.<br><br>**For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.**<br>It is not anticipated that the setting for prescribing comparators and subsequent treatments will differ from the intervention, as the intervention will primarily be prescribed in primary care.<br><br>**Would fezolinetant be a candidate for managed access?**<br>It is anticipated that routine commissioning should be achievable for fezolinetant and therefore it would not be considered a likely candidate for managed access. Additionally, it is anticipated that fezolinetant will primarily be prescribed in primary care.<br><br>**Do you consider that the use of fezolinetant can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br>**Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.**<br>Untreated VMS is associated with societal costs due to lost work productivity, which are not captured in the QALY calculation in the NICE Reference Case.[5] Fezolinetant may provide substantial benefits to work productivity and activity impairment (WPAI) which should be taken into consideration. Additional benefits associated with a reduction in sleep disturbance (such as | Equalities Impact Assessment and any potential impact to the guidance will be discussed by committee. |

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| | | through reduced night-time sweating) are also anticipated via the PROMIS SD SF 8b measure.<br><br>**NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:**<br>• **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which fezolinetant will be licensed;**<br>• **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**<br>• **could have any adverse impact on people with a particular disability or disabilities.**<br>**Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.**<br>Equality considerations are addressed in detail under the Equality section.<br><br>There is a substantial unmet need for treatment options for women with VMS associated with menopause and historically there has been a lack of new innovation in this area of women's health. New treatment options would therefore be welcome to this patient group.<br><br>In addition, Astellas has been advised by UK clinical experts that there are differences in the prevalence and severity of VMS between ethnicities and socioeconomic levels; [1] evidence suggests that VMS is generally more | |

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| | | prevalent in black and Hispanic women, as well as more severe for working class women. [1, 3]<br><br>We also refer back to our previous response in the equality section relating to primary vs. secondary prescribing of fezolinetant and the access inequalities this could help alleviate. | |
| | British Menopause Society (BMS) | These are suitable questions. I would hope that fezolinetant would be able to be prescribed in primary care to enable fair access to the drug. Currently is only available privately. If has to be prescribed by secondary care, the waiting lists for NHS menopause specialists are very long and don't cover all areas of the country. All the other non-hormonal prescribed options are available in primary care but many HCPs are not aware of these options for suitable menopausal patients, particularly those with a hormone sensitive cancer.(JB)<br><br>. | Thank you for your comments. |
| Additional comments on the draft scope | Astellas Pharma Ltd | None | Thank you |
| | British Menopause Society (BMS) | There is an existing ICER publication of relevance to your review:<br>Beaudoin FL, McQueen RB, Wright A, Yeung K, Moradi A, Herron-Smith S, Gutierrez E, Rind DM, Pearson SD, Lin GA. Fezolinetant for Moderate to Severe Vasomotor<br>Symptoms Associated with Menopause: Effectiveness and Value; Final Evidence Report. Institute for<br>Clinical and Economic Review, January 23, 2023.<br>https://icer.org/assessment/vasomotor-symptoms-menopause-2022/#overview<br>This utilises a decision analytic model to evaluate fezolinetant compared with no pharmacologic treatment, and undertakes an economic analysis. It concludes "At a placeholder price of $6,000 annually, fezolinetant exceeds commonly accepted cost-effectiveness benchmarks. Results suggest that | Thank you |

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| | | fezolinetant would meet these benchmarks and be considered cost-effective if priced around $2,000 annually" so it will be interesting to see where the manufacturers pitch their pricing for the NHS. (MD) | |

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

Bayer

## References


1. Green R, Santoro N. Menopausal symptoms and ethnicity: the Study of Women's Health Across the Nation. Women's Health 2009;5:127-133.
2. Harlow SD, Burnett-Bowie S-AM, Greendale GA, et al. Disparities in reproductive aging and midlife health between Black and White women: the Study of Women's Health Across the Nation (SWAN). Women's midlife health 2022;8:1-17.
3. Fawcett. Menopause and the Workplace. Available at: https://www.fawcettsociety.org.uk/menopauseandtheworkplace [Accessed 06 June 2023].
4. Umland EM, Falconieri L. Treatment options for vasomotor symptoms in menopause: focus on desvenlafaxine. International Journal of Women's Health 2012:305-319.
5. Sarrel P, Portman D, Lefebvre P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. Menopause 2015;22:260-266.