7.02 FEZOLINETANT, Tablet 45 mg, Veoza®, ASTELLAS PHARMA AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The standard re-entry resubmission requested Authority Required (Streamlined) listing for fezolinetant (Veoza®) 45 mg for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause in patients unsuitable for menopausal hormone therapy (MHT) due to contraindication (MHT contraindicated), treatment cessation (MHT stopper) or risk versus benefit safety concerns (MHT cautioned). The PBAC considered fezolinetant for the same indication in patients unsuitable for MHT (including those unwilling to take MHT (i.e. MHT averse)) at the March 2025 PBAC meeting.

1.2 Listing was requested on the basis of a cost-utility analysis versus placebo (no treatment). The basis of the listing was unchanged from the March 2025 submission. Table 1 summarises the components of the overall clinical claim addressed by the resubmission.

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Post-menopausal women experiencing moderate to severe vasomotor symptoms (VMS) who are unsuitable for MHT due to contraindications, treatment cessation (stopper), or risk versus benefit safety concerns (caution).
Intervention	Fezolinetant 45 mg oral tablet once daily (monotherapy),
Comparator	No treatment, represented by placebo in the key clinical trial as the proposed relevant comparator,
Outcomes	Primary outcomes: - Change from baseline in frequency and severity of moderate to severe VMS at Week 4 and Week 12 (SKYLIGHT), and Week 24 (DAYLIGHT). Key secondary outcomes: - Menopause-specific quality of life (MENQOL) - Sleep disturbance (PROMIS-SD SF 8b) - Work productivity (WPAI-VMS) - Patient-reported global impression of change (PGI-C VMS, PGI-S SD) - EQ-5D-5L; PHQ-4
Clinical claim	Fezolinetant 45 mg is superior in effectiveness compared to no pharmacologic treatment, with a manageable safety profile as demonstrated in Phase 3 trials (DAYLIGHT; SKYLIGHT 1, 2, 4).

Source: Table 1.1-1, p4 of the resubmission.
EQ-5D-5L=Euro-Qol-5D-5L; MHT=menopausal hormone therapy; PGI-S SD=Patient Global Impression of Severity in Sleep Disturbance; PGI-C VMS=Patient Global Impression of Change in Vasomotor Symptoms; PHQ-4=Patient Health Questionnaire for Anxiety and Depression; PROMIS-SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b; WPAI-VMS=Work Productivity and Activity Impairment for Vasomotor Symptoms
Blue shading indicates data previously seen by the PBAC.

2 Background

Registration status

2.1 Fezolinetant 45 mg was registered by the TGA on 26 February 2024 for the following indication: "VEOZA is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause."

2.2 The resubmission stated the product information (PI) was being reviewed by the TGA for changes that included recommendations for hepatoxicity and liver function monitoring. These changes were finalised and the PI revised on 29 August 2025, prior to the PBAC's consideration of the resubmission.

Previous PBAC consideration

2.3 At the March 2025 meeting, the PBAC did not recommend fezolinetant for the treatment of moderate to severe menopause-related VMS. The PBAC considered that the clinical place for fezolinetant was not well-defined and the proposed population eligible for fezolinetant was broader than is clinically appropriate, including patients who could be treated with MHT. The PBAC noted the increasing safety concern of drug-induced liver disease with the use of fezolinetant since TGA approval in May 2024, and that this had not been adequately addressed in the submission. In addition, the PBAC considered that the incremental cost-effectiveness ratio (ICER) and financial impact of listing fezolinetant were unacceptably high (paragraphs 7.1, 7.11 and 7.13, fezolinetant Public Summary Document [PSD] March 2025 PBAC meeting).

2.4 Fezolinetant for moderate to severe VMS associated with menopause was recently considered by other Health Technology Assessment (HTA) Committees. The UK National Institute for Health and Care Excellence (NICE) March 2025 draft guidance[1] recommended that fezolinetant should not be used to treat moderate to severe VMS caused by menopause. The NICE UK draft guidance stated that there is not enough evidence to determine whether fezolinetant is value for money, noting the lack of robust evidence to show how moderate to severe VMS changed over time and uncertainties in the economic model (with respect to VMS symptoms important to patients, impact of treatment on severity of these symptoms and the eligible population) to estimate the cost-effectiveness of fezolinetant compared to other treatment options.

2.5 Table 2 presents a summary of key matters of concern raised by the PBAC at the March 2025 meeting and how the matters were addressed in the resubmission.

[1] National Institute for Health and Care Excellence (NICE). Draft guidance consultation - Fezolinetant for treating moderate to severe vasomotor symptoms caused by menopause. March 2025. Available from: https://www.nice.org.uk/guidance/gid-ta11058/documents/html-content-7. Accessed on 15/07/2025.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Requested price	The requested price for fezolinetant (AEMP $[redacted] and DPMQ $[redacted]) was higher than the current private market price (~$70) (para 7.10, fezolinetant ratified minutes March 2025).	The resubmission requested a Special Pricing Arrangement for fezolinetant with an effective AEMP $[redacted] (DPMQ $[redacted]), representing a [redacted]% reduction on the previous submission.
Restriction and Clinical place for proposed therapy	The PBAC considered that the requested restriction would not limit first-line access to patients with medical reasons to avoid MHT. It would be essential to more clearly articulate sub-populations 'unsuitable for MHT' in order to exclude patients without a medical reason to avoid MHT. The PBAC considered that definitions for "MHT caution" and "MHT contraindication" should be explicit (e.g. as defined in the Toolkit and Guidelines), rather than referring to product information (PIs) for MHT. The PBAC considered that the population and listing may require further refinement, but it may be appropriate to include (para 7.4, fezolinetant PSD March 2025): • First-line treatment for moderate to severe menopause-related VMS in patients with a MHT contraindication. • Treatment for patients who discontinued MHT due to side effects. • Treatment for patients with a high risk of breast or endometrial cancer. • Second-line treatment after at least 3 months trial of transdermal MHT if comorbidities have been exacerbated by MHT. The PBAC also considered with regard to the restriction (para 7.5, fezolinetant PSD March 2025): • It was unclear if it would exclude perimenopausal women. The PBAC noted that some perimenopausal women also experience VMS, but that these patients were excluded from clinical trials. • It would be appropriate to define moderate to severe VMS, consistent with definitions in guidelines. • It would be appropriate to add a caution regarding hepatotoxicity and recommended LFT. • A written or telephone authority required listing may be more appropriate for initial treatment to ensure that treatment is limited to the intended population.	The PBS restriction was revised with clinical criteria indicating patients must be MHT unsuitable (excluding MHT averse) due to one of the following: • MHT contraindicated (refer to MHT PI for contraindications); • Discontinued MHT due to side effects, poor tolerability or lack of efficacy; • Has an underlying condition which requires special caution to MHT (including history of diabetes, hyperlipidaemia, smoking, migraine, obesity, systemic lupus erythematosus, epilepsy, history of breast cancer or mutation of breast cancer gene (BRCA1 and BRCA2)). The resubmission presented the TGA PI with revisions to include recommendations for hepatoxicity and liver function monitoring (Attachment 01 of the resubmission). The revised TGA PI recommends evaluating hepatic function before initiating therapy. Then follow-up evaluation of hepatic function monthly for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement. Patients are recommended to discontinue fezolinetant if they experience hepatoxicity or increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels.

Component	Matter of concern	How the resubmission addresses it
Comparator	The PBAC considered that the nomination of 'no treatment' as the main comparator is not appropriate for the requested PBS patients who are contraindicated to MHT, or who have discontinued MHT due to adverse effects (AEs). The PBAC noted that there are a number of non-hormonal medicines currently used off-label in Australian clinical practice for treatment of menopause-related VMS (e.g. oxybutynin, gabapentin, propranolol, clonidine, SSRIs), however the submission did not present any evidence for fezolinetant compared to these alternative treatments. The PBAC considered it important to better understand what treatments, if any, are currently used in Australian clinical practice by subpopulations of patients with menopause related VMS. The PBAC also considered that 'no treatment' is not an appropriate comparator where MHT is a clinically appropriate option and patients do not have a medical reason to avoid MHT, even where some patients in this category may choose not to receive MHT in the absence of an alternative. The PBAC considered that while there may be a place for fezolinetant in some "MHT caution" patients, MHT should still be considered as a valid comparator to fezolinetant, as the risks and benefits of MHT in these patients would need to be considered against the risks and benefits of using fezolinetant (para 7.6, fezolinetant PSD March 2025).	Unchanged from the previous submission. The resubmission nominated 'no pharmacologic treatment' as the main comparator for the proposed PBS population who are unsuitable for MHT. However, the restriction wording was amended to restrict use to those medically unsuitable to MHT, which is more aligned with second-line use. The resubmission argued that: • Real world data and clinical advisory consensus statement indicate that non-hormonal treatment options (e.g., SSRI/SNRI, gabapentinoid, oxybutynin) and clonidine are not routinely used, infrequently prescribed, have tolerability concerns and are not PBS-listed or TGA-approved for this indication (see Attachments 1 and 2 of the resubmission). • Placebo (no active treatment) was the comparator in the fezolinetant trials (DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2).
Clinical evidence & clinical claim	The PBAC considered that the claim of superior effectiveness over no treatment was likely supported by the evidence; however, the clinical significance is somewhat uncertain (para 7.8, fezolinetant PSD March 2025). The PBAC considered that, based on the evidence presented, the safety of fezolinetant was inferior compared to placebo. The PBAC noted that the PSUR (July 2024) reported that fezolinetant was associated with symptomatic hepatotoxicity and the PSCR noted the sponsor will be updating the TGA approved PI with a recommendation for follow-up monitoring of liver function. However, the PBAC considered that symptomatic hepatotoxicity was a concern, particularly given the limited safety data beyond 52 weeks. The PBAC considered that monitoring of LFTs is potentially onerous for patients to comply with, and some patients may avoid LFTs until symptomatic. As such, stronger regulation or Quality Use of Medicines activities may be needed (para 7.9, fezolinetant PSD March 2025).	The resubmission presented additional *post hoc* analysis in the revised PBS population who are MHT unsuitable (excluding MHT averse) from DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2. The efficacy and safety results were similar between patients who were MHT unsuitable (excluding MHT averse) versus MHT unsuitable (including MHT averse), as presented in the previous submission. The clinical claim was unchanged. The resubmission did not address the symptomatic hepatoxicity concerns, but provided an updated draft PI, which includes additional recommendations regarding monitoring of liver function. The resubmission maintained fezolinetant as superior in terms of effectiveness and manageable (non-inferior) safety compared to placebo (no treatment).

Component	Matter of concern	How the resubmission addresses it
Economic evaluation	The PBAC considered that the ICER of $[redacted][1]/QALY was unacceptably high given the level of uncertainty associated with the modelled outcomes and the potentially relatively large patient population. The PBAC considered that the price would need to be substantially reduced to realise an ICER in the range of $[redacted][2] to $[redacted][3] per QALY, which the PBAC considered would be more acceptable in the context of the uncertain benefit and the overall financial impact of listing fezolinetant in a revised patient population (para 7.11, fezolinetant ratified minutes March 2025).	Largely unchanged from the previous submission. The modelled economic evaluation was revised, incorporating: • Proposed effective price (AEMP was reduced from $[redacted] to $[redacted]/pack) • LFT cost • Updated health state cost and resource use to more recently available (2023-2024). Efficacy and utility data in MHT unsuitable population (including MHT averse) were unchanged from the previous submission and assumed for the revised PBS population who are MHT unsuitable (excluding MHT averse) given comparable results in the additional *post hoc* analysis. The resubmission estimated ICER for fezolinetant versus no treatment was $[redacted][3]/QALY gained.
Financial estimates	The PBAC considered the financial estimates of $[redacted][4] over 6 years to be uncertain, unacceptably high, and likely substantially overestimated for the requested population. The PBAC agreed with the DUSC that the utilisation and financial estimates were complex and required substantial changes, including (para 7.13, fezolinetant ratified minutes March 2025): Revision of the patient population to align with a substantially more restricted population. The assumption of 75% of Australian women 'unsuitable for MHT' is substantially overestimated (even if the 'MHT adverse' category is included). The PBAC considered that the patient population with the highest need for non-hormonal treatments for VMS (cancer patients with pharmacologically induced menopause) is likely to be much smaller. The uptake rate for fezolinetant was uncertain, and likely to be overestimated given hepatoxicity concerns and the need for liver function monitoring. The discontinuation rate applied as an annual compliance rate was not appropriate and did not reflect patients discontinuing treatment being removed from the pool of prevalent patients. Substitution of fezolinetant for MHTs and its market implications were not considered. The PBAC considered that the availability of a PBS-listed non-hormonal may impact treatment decisions regarding risks and benefits of MHT, and therefore, fezolinetant would substitute for MHT for some patients. Additionally, tests and care costs should be included.	The financial estimates were revised, incorporating: • Proposed effective price • Revised PBS restriction • PBS population who are post-menopausal aged 40-65 years • Assumed 45.04% MHT unsuitable (excluding MHT averse) would be eligible for fezolinetant • Annual discontinuation of 27.4%; annual compliance of 77.9%. • Assumed uptake rates in Year 1: [redacted]%, Year 2: [redacted]%, Year 3: [redacted]%, Year 4: [redacted]%, Year 5: [redacted]% and Year 6: [redacted]%. • Removed MBS cost savings (GP visit and specialist visit) • Added MBS costs for LFTs The resubmission estimated a total net cost to PBS/RPBS of $[redacted][5] over the first 6 years of use.

Component	Matter of concern	How the resubmission addresses it
RSA	The PBAC considered that an RSA is likely to be essential to manage risks of usage outside the revised PBS restriction, usage beyond expectations (e.g. average treatment durations longer than those in the trials), and uncertainty around the percentage of Australian women eligible for treatment (para 7.14, fezolinetant PSD March 2025).	The resubmission proposed an RSA for fezolinetant under a single arrangement with tiered subsidisation cap: [redacted]% rebate if PBS/RPBS expenditures between >[redacted]% and ≤[redacted]% of cap; [redacted]% rebate if PBS/RPBS expenditures between >[redacted]% and ≤[redacted]% of cap; and [redacted]% rebate if PBS/RPBS expenditures between >[redacted]% and ≤[redacted]% of cap.

Source: Summary Table of Changes/Updates in Section 1, pp1-2, Section 2, p19, Section 3, p67, Section 4, pp103-104 of the resubmission.
LFT=liver function test; MHT=menopausal hormone therapy; RSA=risk share arrangement; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor.
Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$15,000 to < $25,000*
[3] *$25,000 to < $35,000*
[4] *$800 million to < $900 million*
[5] *$200 million to < $300 million*

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FEZOLINETANT					
Fezolinetant 45 mg film-coated tablet, 30	$[redacted] published price $[redacted] effective price	1	30	5	VEOZA
Category / Program: General Schedule					
Restriction type: ☒Authority Required (STREAMLINED)					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Caution:					
Baseline hepatic laboratory tests should be performed for all patients before initiating fezolinetant. Follow-up hepatic laboratory tests should be performed monthly for the first 3 months, at 6 months and 9 months of therapy.					
Severity: Moderate to severe					
Condition: Menopause-related vasomotor symptoms (VMS)					
Indication: Moderate to severe menopause-related vasomotor symptoms (VMS)					
Treatment Phase: Initial and continuing					
Clinical criteria:					
Patient must be unsuitable to receive menopausal hormone therapy *(MHT)* due to experiencing at least one of the following:					

~~i)~~ has a condition for which ~~menopausal hormone therapy~~ *MHT* is contraindicated ~~(refer relevant hormone replacement therapy Product Information for conditions for which therapy is contraindicated)~~. **~~OR~~** ii) has discontinued ~~menopausal hormone therapy~~ *MHT* due to side effects*/ ~~of the medicine~~* poor tolerability. ~~or~~ ~~iii)~~ *has discontinued MHT after at least 3 months of therapy due to* lack of efficacy. **~~OR~~** ~~iv) has underlying medical condition which requires special caution in regard to menopausal hormone therapy. This includes:~~ ~~a. history of diabetes mellitus,~~ ~~b. hyperlipidaemia,~~ ~~c. smoking (current),~~ ~~d. migraine,~~ ~~e. obesity (body mass index >29.9 kg/m2),~~ ~~f. systemic lupus erythematosus,~~ ~~g. epilepsy,~~ h. ~~family history of breast cancer in the first degree relative or mutation of breast cancer gene (BRCA1 and BRCA2)~~
~~Administrative Advice~~ ***Treatment criteria*:**
~~For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner.~~ *Must be treated by a health practitioner who is any of:* (i) *a medical practitioner,* (ii) *a nurse practitioner who is continuing treatment with this medicine (of any strength) that was initiated by a medical practitioner as a PBS benefit.*
Prescribing Instructions:
For patients with either a contraindication or caution to systemic MHT, transdermal MHT should be considered prior to receiving treatment with this drug.
Prescribing Instructions:
A contraindication to systemic menopausal hormone therapy (MHT) is defined as at least one of the following: *(i) age 60 years or older, (unless already on MHT and reassessed)* *(ii) previous venous thromboembolism,* *(iii) previous transient ischaemic attack, stroke or acute myocardial infarction,* *(iv) uncontrolled hypertension,* *(v) estrogen-dependent cancer (e.g., endometrial or breast cancer),* *(vi) undiagnosed vaginal bleeding (may include estrogen-dependent cancer),* *(vii) high risk of breast cancer after individual risk assessment.* *(viii) significant liver disease,* *(ix) porphyria or systemic lupus erythematosus (may be exacerbated by estrogen)*
Caution: Fezolinetant is intended for use in postmenopausal women

Source: Table 1.4-1, p14, Table ES-2, ppiv-v of the submission, and p5 of the Pre-PBAC response.
Blue shading indicates data previously seen by the PBAC.
Italics indicates additions proposed by the sponsor in the Pre-PBAC response.
Strikethrough indicates deletions proposed by the sponsor in the Pre-PBAC response.

3.1 The resubmission requested Authority Required (Streamlined) listing of fezolinetant 45 mg, consistent with the March 2025 submission. In the March 2025 meeting, the PBAC considered that a written or telephone authority required listing may be more appropriate for initial treatment to ensure that treatment is limited to the intended population (paragraph 7.5, fezolinetant PSD March 2025 PBAC meeting).

3.2 The resubmission proposed a Special Pricing Arrangement (SPA) for fezolinetant. The proposed effective DPMQ $[redacted] (AEMP $[redacted]) was [redacted]% lower than the proposed published DPMQ $[redacted] (AEMP $[redacted]), which was the same proposed price in the March 2025 submission. The PBAC previously considered that the price of fezolinetant would need to be substantially reduced to achieve acceptable cost-

effectiveness (paragraph 7.11, fezolinetant PSD March 2025 PBAC meeting). The evaluation and the ESC noted that the requested effective DPMQ remains higher than the current private market price for fezolinetant 45 mg in Australia ($70[2]).

3.3 In the resubmission the requested restriction was modified following comments by the PBAC in March 2025 (paragraphs 7.4 and 7.5, fezolinetant PSD March 2025 PBAC meeting). These changes included:

- Clinical criteria wording for patients who discontinued MHT (MHT stoppers) to include "poor tolerability" as a reason for ceasing MHT.
- Additional criteria for patients with underlying medical conditions that require special caution in regard to MHT (MHT caution). This included: history of diabetes mellitus, hyperlipidaemia, current smoker, migraine, obesity, systemic lupus erythematosus, epilepsy and family history of breast cancer in the first degree relative or mutation of breast cancer gene (BRCA1 and BRCA2).
- Removal of the clinical criteria for patients unwilling to take MHT following education on the risks and benefits of treatment.
- Additional caution wording that fezolinetant is intended for use in post-menopausal women.

3.4 The evaluation and the ESC considered that while the restriction limited use to patients who are MHT unsuitable (defined as MHT contraindicated, MHT stopper or MHT cautioned, and excluding MHT averse patients), the requested restriction criteria would likely permit broader use of fezolinetant than intended. The following issues were noted by the evaluation and the ESC regarding the restrictions proposed in the resubmission. The restriction above includes revisions as proposed in the pre-PBAC to address some of these issues:

- The requirement for patients to have moderate to severe VMS was not defined. The PBAC previously considered it would be appropriate to define moderate to severe VMS, consistent with the definitions in guidelines (paragraph 7.5, fezolinetant PSD March 2025 PBAC meeting). The US Food and Drug Administration (FDA)[3] defined moderate VMS as a sensation of heat with sweating, able to continue activity and severe VMS as a sensation of heat with sweating, causing cessation of activity. This was also the definition used in the clinical trials. The ESC noted that it is unclear whether patients with mild symptoms are likely to seek treatment, though increasing awareness of menopause and peri-menopause may increase the number of patients seeking treatment. The PBAC noted that input

[2] $69.99 at Chemist Warehouse - https://www.chemistwarehouse.com.au/search?searchtext=veoza&fh=1

[3] The FDA defined moderate VMS as a sensation of heat with sweating, able to continue activity and severe VMS as a sensation of heat with sweating, causing cessation of activity. Symptom severity is calculated as a weighted average of individual episode severities over a specified period (i.e. one week). Center for Drug Evaluation and Research (CDER). Guidance for Industry. Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation. Food and Drug Administration (FDA), USA, 2023.

from clinicians provided as a written statement indicated they were supportive of inclusion of a definition of moderate-severe VMS in the restrictions and supportive of the FDA definition. These comments suggested the restrictions should include patients experiencing an average of ≥ 7 moderate-to-severe hot flushes per day, as an objective measure of disease severity, which was consistent with the inclusion criteria in the trials.

- The criteria for patients with conditions that contraindicate MHT were not explicitly defined as per previous PBAC consideration, and were instead based on the PI for MHT. The Pre-PBAC response accepted the additional prescribing instruction proposed by the Secretariat, with the addition of an additional point (vii) regarding risk of breast cancer:

"A contraindication to systemic menopausal hormone therapy (MHT) is defined as at least one of the following:

(i) age 60 years or older, (unless already on MHT and reassessed)
(ii) previous venous thromboembolism,
(iii) previous transient ischaemic attack, stroke or acute myocardial infarction,
(iv) uncontrolled hypertension,
(v) estrogen-dependent cancer (e.g., endometrial or breast cancer),
(vi) undiagnosed vaginal bleeding (may include estrogen-dependent cancer),
(vii) high risk of breast cancer after individual risk assessment.
(viii) significant liver disease,
(ix) porphyria or systemic lupus erythematosus (may be exacerbated by estrogen)"

- The revised restriction included a note of caution that fezolinetant is intended for use in post-menopausal women. However, it does not exclude perimenopausal patients experiencing VMS from accessing treatment through the PBS. Since the key trials included only post-menopausal patients and excluded perimenopausal participants, the long-term safety and efficacy of fezolinetant in perimenopausal patients remain uncertain.

- The clinical criteria included a criterion for "underlying medical condition which requires special caution in regard to menopausal hormone therapy", but did not include a clinical assessment for the risk to MHT or a trial of transdermal MHT, as previously recommended by the PBAC (paragraph 7.4, fezolinetant PSD March 2025 PBAC meeting). The ESC considered that the inclusion of patients with "MHT caution" would still capture a large number of patients who could be appropriately treated with oral or transdermal MHT. The ESC considered it would be more appropriate to remove the revised restriction regarding "MHT caution", which was agreed in the Pre-PBAC response .

- The resubmission restriction did not require patients with caution for MHT, due to risks associated with oral oestrogen, to trial transdermal MHT for at least 3 months before being eligible for fezolinetant if their comorbidities have worsened due to MHT. The PBAC previously noted that the cautions other than high risk of breast or endometrial cancer are related to oral, rather than transdermal oestrogen

(paragraph 7.4, fezolinetant PSD March 2025 PBAC meeting). The Pre-PBAC response included a new prescribing instruction "For patients with either a contraindication or caution to systemic MHT, transdermal MHT should be considered prior to receiving treatment with this drug", as proposed by the Secretariat.

- The restriction did not specify any assessment or monitoring requirements, arguing that monitoring, such as liver function tests (LFTs) and symptom severity assessment post-treatment, would be guided by the revised fezolinetant PI. However, the PBAC had previously considered that it would be appropriate to add a caution to the restriction regarding hepatotoxicity and recommended LFT monitoring (paragraph 7.5, fezolinetant PSD March 2025 PBAC meeting). The Pre-PBAC response supported the inclusion of hepatic-monitoring requirements within both the PI and PBS restriction. The sponsor advised that the TGA PI had been further revised with updated monitoring requirements, mirroring the ESC and Secretariat's recommended wording, and added a caution to the proposed restriction with guidance on liver function testing, as proposed by the Secretariat.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Menopause occurs when ovulatory and related functions end. This natural process is associated with a decrease in reproductive hormone (e.g. ovarian oestrogen) production. Menopause onset is traditionally defined as the time of the last menstrual period. In Australia, the median age at which menopause occurs is 51 years, with a normal range of 45 to 55 years. The hormonal changes at menopause have systemic effects, increasing the risk of cardiovascular disease (CVD), diabetes mellitus, cancers associated with central adiposity, reduced neurological health, bone loss and fragility fracture. VMS (hot flushes and night sweats) are the most common symptoms of menopause. Other symptoms may include urogenital symptoms (e.g. vaginal dryness, dyspareunia, dysuria, nocturia) or sleep disturbance, fatigue, musculoskeletal symptoms or psychological symptoms (e.g. memory/concentration problems, anxiety) (Davis 2023b[4]).

4.2 VMS arise from hypothalamic thermoregulatory dysfunction triggered by declining oestrogen levels. This dysfunction is driven by increased activity of KNDy neurons (kisspeptin–neurokinin B–dynorphin), which disrupts temperature regulation through overstimulation of the thermoregulatory centre. VMS typically begin during the perimenopausal years, peak during early post-menopause, and may persist for a decade or more. The median duration of moderate to severe VMS is between 4 and 7 years, with some women continuing to experience symptoms well into their 70s.

[4] Davis SR, Pinkerton J, Santoro N, Simoncini T. Menopause-Biology, consequences, supportive care, and therapeutic options. Cell. 2023. 186(19):4038-4058.

Moderate to severe VMS are associated with impaired sleep, concentration, psychological and general wellbeing and overall quality of life.

4.3 Fezolinetant is a non-hormonal selective neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on KNDy neurons to modulate neuronal activity in the thermoregulatory centre. The recommended dose of fezolinetant is 45 mg once daily at about the same time each day.

4.4 The PBAC previously noted that MHT, which is less costly than fezolinetant, is the most effective and current mainstay treatment for VMS and other symptoms associated with menopause. Guidelines consistently recommend MHT as the most effective treatment for moderate to severe VMS, menopause-associated mood disturbance, urogenital symptoms and prevention of bone loss and fracture (Hamachandra 20245). Factors affecting choice of MHT include menopausal stage (perimenopause or post-menopause), contraindications, risks versus benefits of treatment, indication (e.g. hysterectomy) or preferences for specific formulations (Therapeutic guidelines Australia 2023[6], Davis 2023a[7]).

4.5 The PBAC also previously noted a number of viable (off-label) non-hormonal treatments that reduce menopause-related VMS, are less costly than fezolinetant, and are in established use for women with contraindications to oestrogen based MHT are available (paragraph 7.1, fezolinetant PSD March 2025 PBAC meeting).

4.6 The proposed clinical management algorithm was changed from the March 2025 submission so that the requested PBS restriction for MHT unsuitable no longer included "MHT averse" patients. The resubmission stated that MHT remains the first-line treatment for moderate to severe VMS in women suitable for MHT, but positioned fezolinetant as an alternative first-line treatment to MHT, determined by patients' unsuitability for MHT. The resubmission noted that the efficacy and safety of fezolinetant in the following patient populations is unknown: aged >65 years; current or previous breast cancer or other oestrogen-dependent tumours; or pharmacologically induced menopause.

4.7 The proposed clinical management algorithm was inclusive of patients in all menopausal stages (peri- and post-menopausal) who experienced moderate to severe menopausal symptoms. At the March 2025 PBAC meeting, it was noted that guidelines state that MHT is safe to use for most peri- and post-menopausal individuals (younger than 60yrs /10yrs after onset of menopause), whereas the long-term safety and efficacy of fezolinetant for perimenopausal patients has not been well-established (paragraph 5.6, fezolinetant PSD March 2025 PBAC meeting). While the restriction would not exclude perimenopausal patients who experience VMS from accessing

[5] Hemachandra C, Taylor S, Islam RM, Fooladi E, Davis SR. A systematic review and critical appraisal of menopause guidelines. BMJ Sex Reprod Health. 2024 Apr 11;50(2):122-138.

[6] Therapeutic Guidelines Australia (eTG). 'Nonhormonal drug therapy for vasomotor symptoms of menopause'. Therapeutic Guidelines Limited 2023. Available from: www.tg.org.au/. Accessed on 18/11/2024.

[7] Davis SR, Taylor S, Hemachandra C, Magraith K, Ebeling PR, Jane F, & Islam RM. The 2023 Practitioner's Toolkit for Managing Menopause. Climacteric. 2023. 26(6):517-536.

treatment on the PBS, only those who were post-menopausal were enrolled in the key trials. The resubmission also assumed that only post-menopausal patients would be treated with fezolinetant in the modelled economic evaluation and the financial estimates.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 Previously, the PBAC considered that the nomination of 'no treatment' was not appropriate for patients who are contraindicated to MHT or who have discontinued MHT due to adverse effects (AEs), given the availability of several non-hormonal medicines currently used off-label in Australian clinical practice for the treatment of VMS (paragraph 7.6, fezolinetant PSD March 2025 PBAC meeting). The resubmission maintained no treatment (represented by placebo in the clinical trials) was the main comparator for fezolinetant, arguing that:

- Real-world prescribing data from Australia, along with a clinical advisory board consensus statement[8], indicate that non-hormonal treatment options, e.g., SSRI/SNRI, gabapentinoid, oxybutynin and clonidine are infrequently prescribed for VMS, have tolerability concerns, and with the exception of clonidine are not PBS-listed or TGA-approved for this indication.
- Placebo (no active treatment) was the control arm in the fezolinetant trials (DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2).

5.2 The ESC noted that the consensus statement advised that non-MHT pharmacologic therapies are infrequently prescribed in general practice, and when offered, are often declined by patients due to concerns about tolerability and off-label use. The consensus statement advised that non-MHT pharmacologic therapies do not represent routine standard care for patients unsuitable for treatment with MHT and patients who are unsuitable for treatment with MHT are most often left untreated in typical general practice.

5.3 The real-world prescribing data presented in the resubmission was commissioned by the sponsor as an analysis of real-world data using primary care electronic records to compare the treatments prescribed for two cohorts (before and after launch of fezolinetant in April 2024) of women aged 45-65 years with diagnosis/symptoms related to VMS. The analysis excluded patients with a diagnosis of depression, anxiety, PTSD, epilepsy, hypertension, or urinary incontinence. The real-world prescribing data showed that of the women who initiate treatment for VMS in general practice, approximately 21-28% were treated with non-hormonal therapies (including 6% on fezolinetant in Cohort 2). However, the ESC noted that these sources do not provide details on the treatment patterns specifically for the eligible PBS patient subgroups and do not capture prescribing in treatment settings other than primary care.

[8] The advisory board included advisors with expertise in gynaecology, endocrinology and general practice.

5.4 The ESC considered that nomination of placebo as a comparator would be reasonable, if the amended circumstance of use for fezolinetant genuinely positions it as a second-line treatment after MHT or in patients with a medical contraindication to MHT (including transdermal MHT). The PBAC previously considered fezolinetant to be a second-line treatment following a minimum of 3 months trial of transdermal MHT (paragraph 7.4, fezolinetant PSD March 2025 PBAC meeting). The ESC considered that non-hormonal treatments were also relevant comparators in up to a third of patients unsuitable for treatment with MHT and considered that this issue was not adequately addressed in the resubmission. The Pre-PBAC response acknowledged that some clinicians may prescribe off-label non-hormonal medicines (e.g. SSRIs/SNRIs, gabapentin, clonidine, oxybutynin) for women who are unsuitable for MHT, but reiterated that these agents have variable efficacy, are frequently limited by tolerability or interaction, and are not TGA-approved for VMS, meaning that women who are unsuitable for MHT are most often left untreated in typical general practice.

5.5 In addition to existing alternatives, future emerging treatments include non-hormonal elinzanetant, a dual neurokinin-1 and neurokinin-3 receptor antagonist. Elinzanetant is currently under review by the TGA[9] for the treatment of moderate to severe hot flashes and night sweats (i.e. VMS) associated with menopause.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item, however the sponsor provided a written statement from eight practising clinicians and contributors to the consensus statement provided with the resubmission, providing clarification on the practical clinical context in which fezolinetant would be prescribed in Australia. The comments affirmed the proposed clinical place for fezolinetant, consistent with the revised population (limited to patients with a contraindication to MHT, and patients who have discontinued MHT due to adverse events or insufficient response). The PBAC noted that the statement was also supportive of inclusion of a definition of moderate to severe VMS in the restrictions as an objective measure of disease severity, as was used in the pivotal studies; patients experiencing an average of ≥ 7 moderate-to-severe hot flushes per day.

Consumer comments

6.2 The PBAC noted and welcomed the input on the resubmission from individuals (26), health care professionals (45) and organisations (4) via the Consumer Comments facility on the PBS website, in addition to comments previously received on the

[9] Therapeutic Goods Administration (TGA). TBC Bayer Australia Ltd (active ingredient: elinzanetant). September 2024. Available from: https://www.tga.gov.au/resources/prescription-medicines-under-evaluation/tbc-bayer-australia-ltd#:~:text=You%20are%20here,Sep%2D2024. Accessed on 17/07/2025.

original submission (paragraph 6.2, fezolinetant PSD March 2025 PBAC meeting). The PBAC noted that comments highlighted the importance of using inclusive language in the restrictions for fezolinetant. The comments described the debilitating impacts of VMS on quality of life, and a range of benefits of treatment with fezolinetant, in particular its suitability for treating VMS in women and those assigned female at birth (AFAB) who are contraindicated to MHT and have no suitable PBS funded treatment options.

6.3 Health professionals described VMS as debilitating and significantly impacting quality of life, and noted that currently non-hormonal treatments (clonidine, venlafaxine, oxybutynin, gabapentin, SSRIs/SNRIs) are being used off-label, with varying success and sometimes debilitating or intolerable side effects. Input noted MHT is effective, but not suitable for all women, especially those with contraindications (e.g., breast cancer survivors). Health professionals considered there is a place in therapy for fezolinetant as an effective, and well-tolerated non-hormonal option for women who truly cannot use MHT (eg those with a history of breast cancer), and considered that side-effects are rare but mostly self-limiting, eg nausea and reversible liver function test abnormalities. The PBAC noted that health care providers described the monitoring of liver function tests in the first three months of commencing treatment as onerous and costly. Individuals described VMS as debilitating, and the associated night sweats as severely impacting sleep and quality of life, including exhaustion and associated impact on mood and relationships. A number of individuals described their experiences with alternative non-hormonal treatment options including oxybutynin, desvenlafaxine and venlafaxine, often noting side-effects or lack of efficacy in relieving their VMS. Individuals also noted the cost of fezolinetant on the private market as a barrier to access and equity.

6.4 The PBAC noted the advice received from The Australian Menopause Society, WellFemme Telehealth Menopause Clinic, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and Inherited Cancers Australia clarifying the likely use of fezolinetant in clinical practice, expressing support for its use in patients contraindicated to MHT. In addition to points noted above the input noted that patients who enter menopause suddenly for medical reasons are frequently young and often experience the earliest, worst, and most prolonged symptoms, yet are often contraindicated to MHT.

Clinical trials

6.5 The clinical data presented in the resubmission were largely unchanged from the March 2025 submission, with the exception of an additional post hoc analysis in the revised PBS population, who are MHT unsuitable, defined as MHT contraindicated, MHT stopper and MHT cautioned (excluding MHT averse from the previous submission).

6.6 The clinical evidence was based on four randomised controlled trials (RCTs) comparing fezolinetant versus placebo (DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4) for treatment of moderate to severe VMS. Details of the trials presented in the submission are provided in Table 3 below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
DAYLIGHT (NCT05033886)	A Phase 3b, Randomised, Double-blind, Placebo-controlled, 24-week Study to Assess the Efficacy and Safety of Fezolinetant in Menopausal Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) and Considered Unsuitable for Hormone Replacement Therapy. Schaudig K, Wang X, Bouchard C, Hirschberg AL, Cano A, Shapiro CMM, Stute P, Wu X, Miyazki K, Scrine L, Nappi RE. Efficacy and safety of fezolinetant for moderate-severe vasomotor symptoms associated with menopause in individuals unsuitable for hormone therapy: phase 3b randomised controlled trial	27 Jun 2024 BMJ 2024; 387:e079525
SKYLIGHT 1 (NCT04003155)	A Phase 3, Randomised, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause. Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P, Thurston RC, English M, Franklin C, Lee M, Neal-Perry G. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study.	24 Feb 2022 Lancet. 2023; 401(10382):1091-1102
SKYLIGHT 2 (NCT04003142)	A Phase 3, Randomised, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause. Johnson KA, Martin N, Nappi RE, Neal-Perry G, Shapiro M, Stute P, Thurston RC, Wolfman W, English M, Franklin C, Lee M, Santoro N. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause: A Phase 3 RCT.	23 Feb 2022 J Clin Endocrinol Metab. 2023; 108(8):1981-1997
SKYLIGHT 4 (NCT04003389)	A Randomised, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause. Neal-Perry G, Cano A, Lederman S, Nappi RE, Santoro N, Wolfman W, English M, Franklin C, Valluri U, Ottery FD. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomised controlled trial.	16 May 2022 Obstetrics & Gynecology. 2023; 141(4):737-747

Blue shading indicates data previously seen by the PBAC.
Source: Table 2.2-1, pp23-24 of the resubmission.

6.7 The key features of the included trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment	Population	Outcome(s)	S3
Fezolinetant vs PBO							
DAYLIGHT	452	P3, MC, R, DB, PC, 24 wks	*Low*	Fezolinetant 45 mg[c] PBO	Aged 40-65, Moderate-severe VMS, MHT unsuitable[a]	1°: VMS frequency 2°: VMS severity, sleep disturbance	✓
SKYLIGHT 1	522	P3, MC, R, DB, PC, 12 wks / 40 wks active extension[b]	*Low*	Fezolinetant 30 mg Fezolinetant 45 mg[c] PBO	Aged 40-65, Moderate-severe VMS	1°: VMS frequency, VMS severity 2°: sleep disturbance	-
SKYLIGHT 2	500	P3, MC, R, DB, PC, 12 wks / 40 wks active extension[b]	*Low*	Fezolinetant 30 mg Fezolinetant 45 mg[c] PBO	Aged 40-65, Moderate-severe VMS	1°: VMS frequency, VMS severity 2°: sleep disturbance	-
SKYLIGHT 4	1830	P3, MC, R, DB, PC, 52 wks	*Low*	Fezolinetant 30 mg Fezolinetant 45 mg[c] PBO	Aged 40-65, Menopausal VMS	1°: safety	-

Source: Table 2.4-1, p28 of the resubmission.

DB=double blind; MC=multi-centre; MHT=menopausal hormone therapy; OL=open label; PBO=placebo; PC=placebo controlled; P3=Phase 3; R = randomised; S3=Section 3 (Economic Evaluation); wks = weeks.

a Categories for MHT unsuitability defined based on contraindicated; caution (based on medical history); stoppers (previous discontinuation of hormone therapy owing to lack of efficacy, side effects, or medical advice); or averse (informed choice not to use hormone therapy after discussion with a clinician).

b After completing 12 weeks of treatment, patients in placebo were re-randomised to fezolinetant 30 mg or 45 mg in the active treatment extension period (without placebo control) through end of study. Patients already on an active treatment continued their assigned dose for the remaining 40 weeks of treatment. The extension period remained blinded to the site personnel and patients.

c Fezolinetant 45mg comprised of one 30 mg and one 15 mg tablet.

Blue shading indicates data previously seen by the PBAC.

6.8 Details of DAYLIGHT, SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 were unchanged from the March 2025 submission. The four RCTs were all multicentre (none in Australia), double-blind and placebo-controlled, comparing fezolinetant (45 or 30 mg) versus placebo for treatment of moderate to severe VMS. SKYLIGHT 1 and SKYLIGHT 2 included an extension where patients in the placebo-controlled arm received fezolinetant (45 mg or 30 mg) after the initial 12-week double-blind period. The resubmission sought PBS listing for fezolinetant 45 mg, which is the dosage registered with the TGA for treatment of VMS.

6.9 The resubmission presented updated baseline characteristics in the revised PBS population who are MHT unsuitable (excluding MHT averse) in DAYLIGHT (n=285; 151 in placebo and 134 in fezolinetant 45 mg), SKYLIGHT 1 and SKYLIGHT 2 pooled (n=458; 229 in placebo and 229 in fezolinetant 45 mg) and SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 pooled for safety (n=1316; 655 in placebo and 661 in fezolinetant 45 mg). In DAYLIGHT, the MHT stopper subgroup was broadly defined as patients who discontinued MHT due to lack of efficacy, MHT-related side effects, advised by healthcare provider to stop due to length of time on MHT or due to age ≥ 60 years. Whereas in the post hoc analyses of SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4, the MHT unsuitable patients included those who stopped MHT due to 'medical concerns' (undefined).

6.10 Baseline characteristics were generally balanced between treatment arms in the included trials, except in DAYLIGHT more patients in the fezolinetant arm had prior hysterectomy compared to placebo (20.3% vs 10.6%). Across the trials, while patients'

baseline characteristics were broadly similar, the evaluation noted some differences, including:

- Race: more Caucasian patients in DAYLIGHT (96.2-98.0%) compared to other trials (75.9-80.6%)
- Medical history of hysterectomy and oophorectomy: fewer patients in DAYLIGHT had previous hysterectomy (10.6-20.3%) and oophorectomy (10.6-12.8%) compared to other trials (27.0-36.8% hysterectomy; 18.9-25.4% oophorectomy)
- MHT history: fewer patients in DAYLIGHT were MHT caution (32.7-40.3%)

6.11 The evaluation considered that across the trials, the baseline demographic and disease characteristics in the revised patient subgroup who are MHT unsuitable (excluding MHT averse) were generally similar to the overall population.

Comparative effectiveness

6.12 With the exception of SKYLIGHT 4, all trials presented changes in frequency and severity of moderate to severe VMS as the primary or secondary outcome after 12/24 weeks of treatment. The primary outcome of SKYLIGHT 4 was the long-term safety of fezolinetant to Week 52.

6.13 The resubmission re-presented the results of the discrete choice experiment (DCE) of patient preferences for the attributes of treatment for moderate to severe VMS. The DCE found that improvement in VMS frequency is the most important factor for preference; VMS severity improvement was less important; sleep disturbance improvement was similar in importance to VMS severity; and the risk of side effects appeared to be the least important factor for preference. The DCE target population sample was Australian women (N=120) aged 40-65 years with menopause and current or previous episodes of moderate to severe VMS (≥7 hot flushes, sensations of heat with sweating over a 24-hour period).

6.14 The resubmission stated that the DCE study did not sample women based on the criteria for MHT unsuitable because it was not practical or reliable to recruit for market research based on these criteria without medical records or physician information. The resubmission also stated that the reason the attributes used for frequency (reduced by at least half) and severity of VMS (number of days reduced with severe and interrupting hot flushes) in the DCE was inconsistent with the trial definition for change in VMS frequency and severity was for “appropriate communication to survey respondents”, whereas the trial definitions were “abstract”. In the trials, VMS frequency was defined as the change from baseline in the average daily number of moderate or severe VMS, and VMS severity was defined as the weighted average of the daily number of VMS by severity (mild, moderate and severe) over a total daily number of VMS.

6.15 The resubmission nominated a minimally clinically important difference (MCID) for improvement in VMS frequency as a reduction of ≥2 moderate to severe VMS episodes per day. The resubmission noted that the FDA and EMA indicated the results

from SKYLIGHT 1 and SKYLIGHT 2 showed statistically significant and clinically meaningful (≥ 2 hot flashes over 24 hours) reduction from baseline in the frequency of moderate to severe VMS for fezolinetant 45 mg compared to placebo at Weeks 4 and 12. This was consistent with the sponsor's claims in the March 2025 pre-PBAC response. The resubmission did not nominate a MCID for improvement in VMS severity, however, the evaluation noted that published studies indicate a reduction >0.225 points at Week 12 on a three-point scale from 1 (mild) to 3 (severe) may be meaningful to post-menopausal women (Constantine 2020[10]). The PBAC previously considered that the impact of reductions in VMS severity and frequency is influenced by a number of factors specific to each individual and their circumstances (e.g. environment and activities being undertaken) (paragraph 7.8, fezolinetant PSD March 2025 PBAC meeting).

Trial results

6.16 Table 5 and Figure 1 present the change from baseline in VMS (frequency and severity) at Week 12/24 (double-blind) to Week 52 (active extension) in the fezolinetant trials. Results below are for the fezolinetant 45 mg and placebo arms.

[10] Constantine GD, Simon JA, Kaunitz AM, Pickar JH, Revicki DA, Graham S, Bernick B, Mirkin S. TX-001HR is associated with a clinically meaningful effect on severity of moderate to severe vasomotor symptoms in the REPLENISH trial. Menopause. 2020. 27(11):1236-1241. doi: 10.1097/GME.0000000000001602.

Table 5: Change from baseline in moderate to severe VMS (frequency and severity) at Week 12/24 in the included fezolinetant trials (double-blind period)

Outcome	FEZ 45 mg	PBO	Difference (95%CI)
LS mean (SE) change from baseline in mean frequency of moderate-severe VMS per 24h[h]			
SKYLIGHT 1, ITT[a], Wk 12[g]	-6.44 (0.31)	-3.90 (0.31)	**-2.55 (-3.40, -1.70)**
SKYLIGHT 2, ITT[a], Wk 12[g]	-7.50 (0.39)	-4.97 (0.39)	**-2.53 (-3.60, -1.46)**
SKYLIGHT 1 & 2 pooled, ITT[a], Wk 12	NR	NR	**-2.51 (-3.20, -1.82)**
DAYLIGHT, MHT unsuitable[b], Wk 12	-7.65 (0.25)	-5.69 (0.25)	**-1.96 (-2.65, -1.26)**
DAYLIGHT, MHT unsuitable[b], Wk 24[g]	-6.20 (0.26)	-8.13 (0.25)	**-1.93 (-2.64, -1.22)**
DAYLIGHT, MHT unsuitable (excluding MHT averse)[d], Wk 24 (post hoc)	-8.04 (0.34)	-6.17 (0.33)	**-1.87 (-2.79, -0.94)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable[c], Wk 12 (post hoc)	-6.97 (0.27)	-4.42 (0.27)	**-2.55 (-3.29, -1.80)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable (excluding MHT averse)[d], Wk 12 (post hoc)	-6.97 (0.30)	-4.22 (0.30)	**-2.75 (-3.59, -1.91)**
DAYLIGHT, SKYLIGHT 1 & 2 pooled, MHT unsuitable, Wk 12 (post hoc)	-7.16 (4.56)[e]	-4.89 (4.39)[e]	**-2.27 (-2.82, -1.72)[f]**
LS mean (SE) change from baseline in mean severity of moderate-severe VMS[i] per 24h[h]			
SKYLIGHT 1, ITT[a], Wk 12[g]	-0.57 (0.05)	-0.37 (0.05)	**-0.20 (-0.35, -0.06)**
SKYLIGHT 2, ITT[a], Wk 12[g]	-0.77 (0.06)	-0.48 (0.06)	**-0.29 (-0.45, -0.13)**
SKYLIGHT 1 & 2 pooled, ITT[a], Wk 12	NR	NR	**-0.24 (-0.35, -0.13)**
DAYLIGHT, MHT unsuitable[b], Wk 12	-0.87 (0.05)	-0.57 (0.06)	**-0.30 (-0.45, -0.15)**
DAYLIGHT, MHT unsuitable[b], Wk 24	-1.01 (0.06)	-0.62 (0.06)	**-0.39 (-0.57, -0.21)**
DAYLIGHT, MHT unsuitable (excluding MHT averse)[d], Wk 24 (post hoc)	-0.99 (0.06)	-0.55 (0.06)	**-0.44 (-0.61, -0.26)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable[c], Wk 12 (post hoc)	-0.71 (0.04)	-0.43 (0.04)	**-0.27 (-0.39, -0.15)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable (excluding MHT averse)[d], Wk 12 (post hoc)	-0.72 (0.05)	-0.41 (0.05)	**-0.31 (-0.45, -0.18)**
DAYLIGHT, SKYLIGHT 1 & 2 pooled, MHT unsuitable, Wk 12 (post hoc)	-0.81 (0.93)[e]	-0.46 (0.79)[e]	**-0.35 (-0.47, -0.23)[f]**

Source: Tables 2.5-1 and 2.5-2, pp34-36, Table 2.8-1, p65, Table 2.5-9, pp45-46, Table 2.5-11, pp47-48 of the resubmission, Table 9.3.2.3, p273, Table 9.3.2.4, p279 of Attachment 07 – DAYLIGHT CSR.pdf, Tables 11 and 12, pp43-45 of Attachment 07 – SKYLIGHT 1 CSR.pdf, Tables 11 and 12, pp45-47 of Attachment 07 - SKYLIGHT 2 CSR.pdf, Table 4 of Santoro 2025 (SKYLIGHT 1 and SKYLIGHT 2 pooled).

CI=confidence interval; FEZ=fezolinetant; LS=least squares; MHT=menopausal hormone therapy; NR=not reported; PBO=placebo; SE=standard error; VMS=vasomotor symptoms; Wk=week;

a In SKYLIGHT 1 and SKYLIGHT 2 patients were not enrolled based on criteria for suitability/unsuitability to receive MHT. Eligible patients had moderate to severe VMS associated with menopause seeking treatment for VMS.

b In DAYLIGHT, enrolled patients were MHT unsuitable defined as contraindicated; caution (based on medical history); stoppers (previous discontinuation due to lack of efficacy, side effects or medical advice); or averse (choice not to use MHT after discussion with clinician).

c In the post hoc analysis of SKYLIGHT 1 and SKYLIGHT 2, MHT history subgroups were mutually exclusive and categorised with the following hierarchy: contraindicated; caution; stopped for medical concerns; averse; naïve/willing. MHT unsuitable group comprised of: contraindicated, caution, stopped for medical concerns or averse subgroups.

d Post hoc subgroup who are MHT unsuitable (included MHT contraindicated, MHT cautioned and MHT stoppers). In DAYLIGHT, the MHT stopper subgroup was broadly defined as patients who discontinued MHT due to lack of efficacy, MHT-related side effects, advised by healthcare provider to stop due to length of time on MHT or due to age ≥ 60 years. For the post hoc analysis of the SKYLIGHT trials, MHT unsuitable included those who stopped MHT due to medical concerns (undefined; without contraindication/caution).

e Reported as mean (SD) change from baseline.

f Mean difference calculated during the evaluation using RevMan v5.3. LS mean difference was not reported in the submission.

g Primary outcome; used in the submission's modelled economic evaluation

h A negative change indicates a reduction/improvement from baseline.

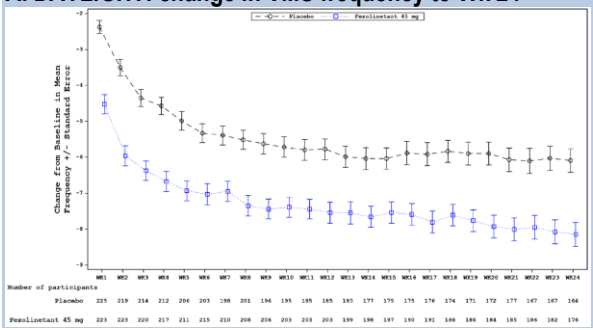
i FDA defined VMS severity: Mild – sensation of heat without sweating; Moderate – sensation of heat with sweating, able to continue activity; and Severe – sensation of heat with sweating, causing cessation of activity.

Blue shading indicates data previously seen by the PBAC.

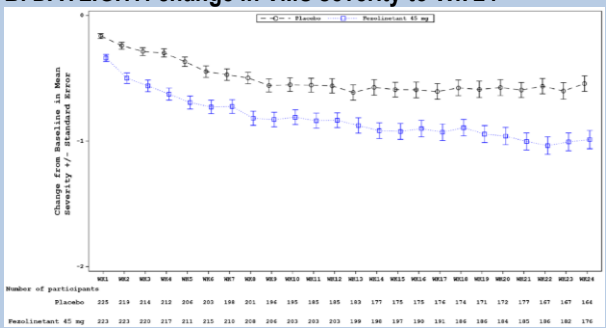
Bold indicates statistically significant results.

Figure 1: Change from baseline in moderate to severe VMS (frequency & severity) to Wk 12/24 (double-blind) to Wk 52 (active extension) in the included fezolinetant trials

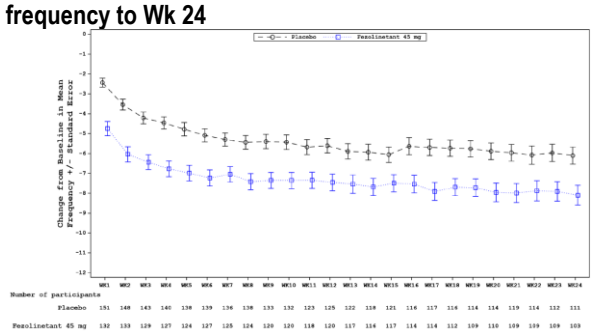
A. DAYLIGHT: change in VMS frequency to Wk 24



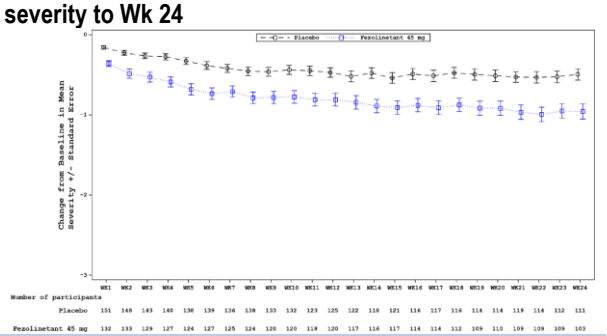
B. DAYLIGHT: change in VMS severity to Wk 24



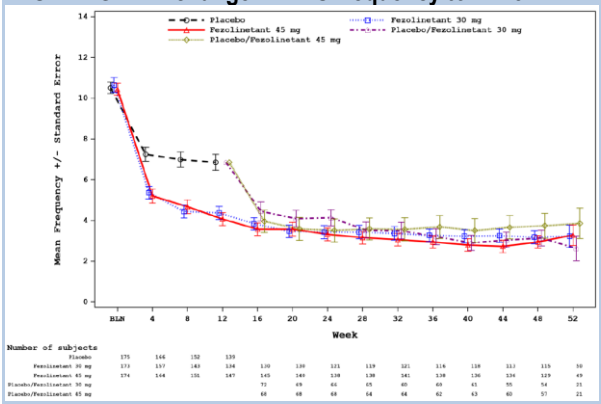
C. DAYLIGHT (exclude MHT averse): change in VMS frequency to Wk 24



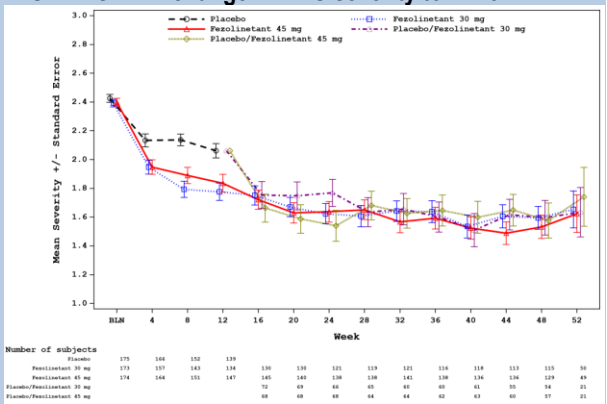
D. DAYLIGHT (exclude MHT averse): change in VMS severity to Wk 24



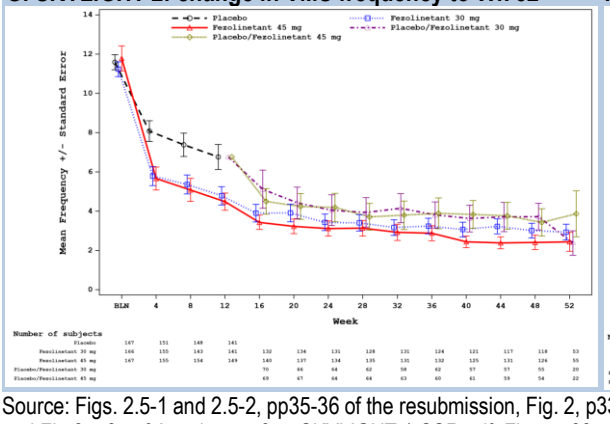
E. SKYLIGHT 1: change in VMS frequency to Wk 52



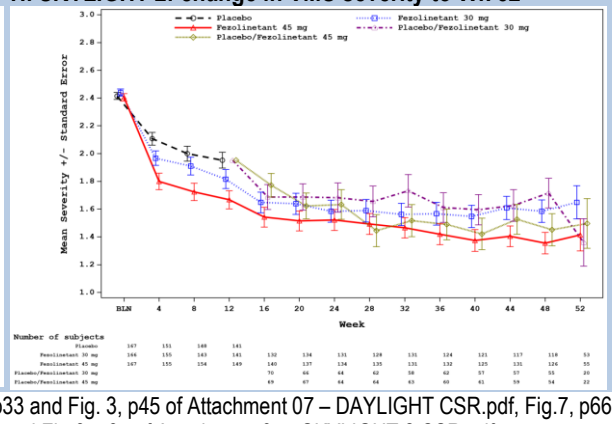
F. SKYLIGHT 1: change in VMS severity to Wk 52



G. SKYLIGHT 2: change in VMS frequency to Wk 52



H. SKYLIGHT 2: change in VMS severity to Wk 52



Source: Figs. 2.5-1 and 2.5-2, pp35-36 of the resubmission, Fig. 2, p33 and Fig. 3, p45 of Attachment 07 – DAYLIGHT CSR.pdf, Fig.7, p66 and Fig.8, p67 of Attachment 07 - SKYLIGHT 1 CSR.pdf, Fig.7, p66 and Fig.8, p67 of Attachment 07 - SKYLIGHT 2 CSR.pdf.
Fig.=figure; MHT=menopausal hormone therapy; VMS=vasomotor symptoms; wk=week.
Blue shading indicates data previously seen by the PBAC.

6.17 Table 6 presents the responder analysis of change from baseline in moderate to severe VMS frequency to Week 12/24 in the fezolinetant trials.

Table 6: VMS frequency response at Week 12/24 in the included fezolinetant trials (double-blind period)

Outcome	FEZ 45mg	PBO	OR (95%CI)
Responders of ≥50% reduction from baseline in mean frequency of moderate-severe VMS per 24h			
SKYLIGHT 1, ITT[a], Wk 12	99/174 (56.9)	52/175 (29.7)	**3.156 (2.035, 4.944)**
SKYLIGHT 2, ITT[a], Wk 12	101/167 (60.5)	71/167 (42.5)	**2.090 (1.351, 3.252)**
SKYLIGHT 1 & 2 pooled, ITT[a], Wk 12	200/341 (58.7)	123/342 (36.0)	**2.542 (1.868, 3.472)**
DAYLIGHT, MHT unsuitable[b], Wk 12	154/226 (68.1)	106/226 (46.9)	**2.422 (1.649, 3.556)**
DAYLIGHT, MHT unsuitable[b], Wk 24	137/226 (60.6)	104/226 (46.0)	**1.815 (1.249, 2.647)**
DAYLIGHT, MHT unsuitable (excluding MHT averse)[d], Wk 24 (post hoc)	72 (54.1)	67 (44.4)	1.483 (0.929, 2.375)
SKYLIGHT 1 & 2 pooled, MHT unsuitable[c], Wk 12 (post hoc)	174/287 (60.6)	106/297 (35.7)	**2.781 (1.991, 3.904)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable (excluding MHT averse)[d], Wk 12 (post hoc)	137 (60.1)	80 (34.9)	**2.806 (1.921, 4.125)**
DAYLIGHT, SKYLIGHT 1 & 2 pooled, MHT unsuitable, Wk 12 (post hoc)	328/513 (63.9)	212/523 (40.5)	**2.623 (2.034, 3.384)**
Responders of ≥75% reduction from baseline in mean frequency of moderate-severe VMS per 24h			
SKYLIGHT 1, ITT[a], Wk 12	60/174 (34.5)	23/175 (13.1)	**3.477 (2.054, 6.055)**
SKYLIGHT 2, ITT[a], Wk 12	66/167 (39.5)	35/167 (21.0)	**2.482 (1.527, 4.089)**
SKYLIGHT 1 & 2 pooled, ITT[a], Wk 12	126/341 (37.0)	58/342 (17.0)	**2.892 (2.026, 4.167)**
DAYLIGHT, MHT unsuitable[b], Wk 12	110/226 (48.7)	66/226 (29.2)	**2.298 (1.559, 3.389)**
DAYLIGHT, MHT unsuitable[b], Wk 24	106/226 (46.9)	67/226 (29.6)	**2.099 (1.427, 3.103)**
DAYLIGHT, MHT unsuitable (excluding MHT averse)[d], Wk 24 (post hoc)	54 (40.6)	43 (28.5)	**1.718 (1.049, 2.828)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable[c], Wk 12 (post hoc)	113/287 (39.4)	53/297 (17.8)	**2.984 (2.046, 4.397)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable (excluding MHT averse)[d], Wk 12 (post hoc)	93 (40.8)	41 (17.9)	**3.144 (2.054, 4.878)**
DAYLIGHT, SKYLIGHT 1 & 2 pooled, MHT unsuitable, Wk 12 (post hoc)	223/513 (43.5)	119/523 (22.8)	**2.618 (1.988, 3.447)**
Responders of 100% reduction from baseline in mean frequency of moderate-severe VMS per 24h			
SKYLIGHT 1, ITT[a], Wk 12	18/174 (10.3)	6/175 (3.4)	**3.262 (1.329, 9.194)**
SKYLIGHT 2, ITT[a], Wk 12	25/167 (15.0)	9/167 (5.4)	**3.049 (1.420, 7.125)**
SKYLIGHT 1 & 2 pooled, ITT[a], Wk 12	42/341 (12.6)	15/342 (4.4)	**3.138 (1.742, 5.953)**
DAYLIGHT, MHT unsuitable[b], Wk 12	49/226 (21.7)	22/226 (9.7)	**2.562 (1.488, 4.412)**
DAYLIGHT, MHT unsuitable[b], Wk 24	50/226 (22.1)	24/226 (10.6)	**2.385 (1.422, 4.098)**
DAYLIGHT, MHT unsuitable (excluding MHT averse)[d], Wk 24 (post hoc)	29 (21.8)	17 (11.3)	**2.193 (1.154, 4.279)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable[c], Wk 12 (post hoc)	37/287 (12.9)	14/297 (4.7)	**2.962 (1.596, 5.795)**
SKYLIGHT 1 & 2 pooled, MHT unsuitable (excluding MHT averse)[d], Wk 12 (post hoc)	28 (12.3)	11 (4.8)	**2.729 (1.354, 5.876)**
DAYLIGHT, SKYLIGHT 1 & 2 pooled, MHT unsuitable, Wk 12 (post hoc)	86/513 (16.8)	36/523 (6.9)	**2.710 (1.788, 4.107)**

Source: Table 2.5-8, p42, Table 2.5-15, pp50-51 of the resubmission, Table 26, pp56-58 of Attachment 07 - DAYLIGHT CSR.pdf, Table 18, pp55-56 of Attachment 07 - SKYLIGHT 1 CSR.pdf, Table 18, pp56-57 of Attachment 07 – SKYLIGHT 2 CSR.pdf, Fig 1 of Nappi 2024 (pooled SKYLIGHT 1 and SKYLIGHT 2).

FEZ=fezolinetant; MHT=menopausal hormone therapy; NR=not reported; OR=odds ratio; PBO=placebo; VMS=vasomotor symptoms; wk=week;

a In SKYLIGHT 1 and SKYLIGHT 2 patients were not enrolled based on criteria for suitability/unsuitability to receive MHT. Eligible patients had moderate to severe VMS associated with menopause seeking treatment for VMS.

b In DAYLIGHT, enrolled patients were MHT unsuitable defined as contraindicated; caution (based on medical history); stoppers (MHT discontinuation due to lack of efficacy, side effects or medical advice); or averse (choice not to use MHT after discussion with clinician).

c In the post hoc analysis of SKYLIGHT 1 and SKYLIGHT 2, MHT history subgroups were mutually exclusive and categorized with the following hierarchy: contraindicated; caution; stopped for medical concerns; averse; naïve/willing. MHT unsuitable group comprised of:

contraindicated, caution, stopped for medical concerns or averse.

d Post hoc subgroup who are MHT unsuitable (included MHT contraindicated, MHT cautioned and MHT stoppers). In DAYLIGHT, the MHT stopper subgroup was broadly defined as patients who discontinued MHT due to lack of efficacy, MHT-related side effects, advised by healthcare provider to stop. For the post hoc analysis of the SKYLIGHT trials, MHT unsuitable included those who stopped MHT due to medical concerns (undefined; without contraindication/caution).

Blue shading indicates data previously seen by the PBAC.

Bold indicates statistically significant results.

6.18 In DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2, the additional post hoc analyses in the MHT unsuitable (excluding MHT averse) patients showed that there was greater improvement (reduction) from baseline in the frequency and severity of moderate to severe VMS for the fezolinetant group compared to placebo at Week 12/24. The improvement (reduction) in VMS frequency and severity was maintained to Week 52 in SKYLIGHT 1 and SKYLIGHT 2 active extension period. Of note, the treatment effect in the placebo arm was high in all trials. The evaluation and the ESC considered that the clinical significance of the difference in VMS frequency was uncertain, given the point estimates for the MHT unsuitable patients with and without MHT averse in DAYLIGHT (-1.87 to -1.96) at Week 12/24 did not meet the MCID (≥2 hot flushes/day), but the point estimates in the overall population (including MHT unsuitable and MHT suitable patients) in SKYLIGHT 1 and SKYLIGHT 2 did (-2.51 to -2.75). However, across the trials for the MHT unsuitable (excluding MHT averse) patients treated with fezolinetant 45 mg, the mean difference versus placebo in the reduction of VMS severity (-0.31 to -0.44) exceeded the MCID for reduction in severity (>0.225 points) at Week 12.

6.19 Across the trials, in the MHT unsuitable (excluding MHT averse) population, the proportion of responders in terms of VMS frequency (≥50%, ≥75% and 100% reduction from baseline) was statistically significantly higher in the fezolinetant arm compared to placebo to Week 12/24, except the DAYLIGHT trial showed no difference between groups in the proportions of responders with ≥50% reduction in VMS frequency.

6.20 The resubmission also presented results of other patient-reported outcomes from DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2. In DAYLIGHT, post hoc MHT unsuitable (excluding MHT averse) patients treated with fezolinetant 45 mg showed improvement from baseline in measures assessing VMS (PGI-C VMS), but there was no difference in sleep disturbance, menopausal and general quality of life (PROMIS SD SF 8b, PGI-S SD, MENQOL and EQ-5D5-L) compared to placebo at Week 24. However, results in the pooled SKYLIGHT 1 and SKYLIGHT 2 post hoc MHT unsuitable (excluding MHT averse) patients showed fezolinetant 45 mg group had improvement from baseline in sleep disturbance, VMS and menopausal quality of life (PROMIS SD SF 8b, PGI, MENQOL) compared to placebo at Week 12.

6.21 Overall, the post hoc analyses in the MHT unsuitable (excluding MHT averse) patients in DAYLIGHT and SKYLIGHT 1 and SKYLIGHT 2 were broadly consistent with results in the overall population in DAYLIGHT who were MHT unsuitable (including MHT averse) and in SKYLIGHT 1 and SKYLIGHT 2 who were MHT suitable or unsuitable (i.e. patients were not enrolled based on MHT unsuitability).

Comparative harms

6.22 Table 7 summarises the adverse events (AEs) from the post hoc pooled SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 trials over 52 weeks.

Table 7: Summary of adverse events in the included trials (double-blind)

AEs, n(%)	DAYLIGHT MHT unsuitable (24w)[c]		SKYLIGHT 1, 2 and 4 MHT unsuitable (excl. MHT averse) (52w)[d]			
	FEZ 45mg N=226	PBO N=226	FEZ 45mg N=659	PBO N=655	PBO/FEZ 45mg N=98	Total FEZ 45mg N=757
Any TEAE	147 (65.0)	138 (61.1)	435 (66.0)	382 (58.3)	57 (58.2)	492 (65.0)
Drug-related TEAE[a]	39 (17.3)	25 (11.1)	110 (16.7)	95 (14.5)	7 (7.1)	117 (15.5)
Serious TEAE	10 (4.4)	8 (3.5)	31 (4.7)	12 (1.8)	5 (5.1)	36 (4.8)
Drug-related serious TEAE	1 (0.4)	0	3 (0.5)	0	1 (1.0)	4 (0.5)
TEAE leading to discontinuation	11 (4.9)	14 (6.2)	30 (4.6)	23 (3.5)	4 (4.1)	34 (4.5)
Death[b]	0	0	0	0	0	0

Source: Tables 2.5-16 and 2.5-17, pp52-53 of the resubmission.

AE=adverse event; FEZ=fezolinetant; MHT=menopausal hormone therapy; PBO=placebo; TEAE=treatment emergent AE;

a Any TEAE with causal relationship assessed by the investigator. If relationship was missing, then it was considered drug-related.

b All reported deaths after the first study intervention administration.

c In DAYLIGHT, enrolled patients were MHT unsuitable defined as contraindicated; caution (based on medical history); stoppers (previous discontinuation due to lack of efficacy, side effects or medical advice); or averse (choice not to use MHT after discussion with clinician).

d The post hoc analysis of the SKYLIGHT trials in patients who are MHT unsuitable included MHT contraindicated, MHT cautioned and MHT stoppers (i.e. stopped MHT due to medical concerns (undefined; without contraindication/caution)).

6.23 In the pooled SKYLIGHT 1, SKYLIGHT 2 and SKYLIGHT 4 post hoc MHT unsuitable (excluding MHT averse) patients, the incidences of any AEs, drug-related AEs, serious AEs and AEs leading to discontinuation were similar between fezolinetant and placebo treatment arms to Week 52. The evaluation considered that the safety results in the MHT unsuitable (excluding MHT averse) subgroup were consistent with the results in the overall population. Across the trials, there were no treatment related deaths.

6.24 The resubmission reported that endometrial hyperplasia (plus AE of endometrial adenocarcinoma for one patient) or malignancy was observed in the fezolinetant 45 mg group (n=2) and none in the placebo group. The incidence of disordered proliferative pattern was similar between groups (1 in fezolinetant 45 mg and 1 in placebo).

6.25 The Periodic Safety Update Report (January 2025) provided updates to international product labels following post-marketing hepatic events, including enhanced liver function monitoring and revised treatment guidance. No new safety concerns were identified for the reporting period from 12 May 2024 to 11 Nov 2024. The PBAC previously noted that the PSUR (July 2024) reported that fezolinetant was associated with symptomatic hepatotoxicity, and that the Pre-Sub-Committee Response (PSCR) noted that the sponsor would be updating the TGA approved PI with a recommendation for follow-up monitoring of liver function. The PBAC previously considered that symptomatic hepatotoxicity was a concern, particularly given the limited safety data beyond 52 weeks (paragraph 7.9, fezolinetant PSD March 2025 PBAC meeting). The resubmission provided the TGA PI with revisions to include recommendations for hepatoxicity and liver function monitoring. The revised TGA PI recommends evaluating hepatic function before initiating therapy, then follow-up

evaluation of hepatic function monthly for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement. Patients are recommended to discontinue fezolinetant if they experience hepatoxicity or increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels.

Benefits/harms

6.26 A benefits and harms table was not presented because the resubmission only presented post hoc results for a revised subgroup who were MHT unsuitable (excluding MHT averse), and the findings are largely unchanged from the March 2025 submission. The evaluation noted that based on the post hoc analysis in DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 at Week 12/24, approximately 2 to 3 fewer patients would experience moderate to severe VMS per 24 hours; the evaluation considered that these differences may be clinically meaningful given some estimates met the MCID for reduction in frequency (≥2 hot flushes/day). Approximately 25 additional patients would experience at least 50% reduction in the frequency of moderate to severe VMS episodes and approximately 12 to 23 additional patients would experience at least 75% reduction in the frequency of moderate to severe VMS episodes. The resubmission did not present comparative safety data in the revised subgroup who were MHT unsuitable (excluding MHT averse) from DAYLIGHT, SKYLIGHT 1 and SKYLIGHT 2 to allow for a quantitative comparison of the harms of treatment between fezolinetant and placebo at Week 12/24.

Clinical claim

6.27 In patients with moderate to severe VMS associated with menopause and unsuitable for MHT (excluding MHT averse), the resubmission described fezolinetant 45 mg as superior in terms of effectiveness compared with no treatment (placebo) and manageable safety compared to no treatment (placebo). The clinical claim was unchanged from the March 2025 submission.

6.28 In March 2025, the PBAC considered that the claim of superior effectiveness over no treatment was likely supported by the evidence, however placebo was not the appropriate comparator for many patients who would be eligible for fezolinetant under the proposed restriction criteria. Further, the PBAC stated that the clinical significance of the effect is somewhat uncertain, noting reductions in VMS frequency met the MCID of >2 VMS per day, but not >3.57 VMS per day (from previous studies of MHT for VMS), and the impact of reductions in VMS severity and frequency is influenced by a number of factors specific to each individual and their circumstances (e.g. environment and activities being undertaken) (paragraphs 6.37 and 7.8, fezolinetant PSD March 2025 PBAC meeting).

6.29 Overall, the evaluation considered that the clinical claim of superior effectiveness of fezolinetant compared with no treatment was likely supported by the evidence presented in the resubmission. The evaluation noted that there were inconsistencies between the trial definition of MHT contraindicated, MHT stopper compared to the requested PBS restriction criteria. However *post hoc* analyses suggested similar efficacy in the subgroup compared to the ITT population.

6.30 The PBAC previously considered that, based on the evidence presented, the safety of fezolinetant was inferior compared to placebo. The PBAC noted that the incidence of AEs was similar between fezolinetant and placebo, except for the risk of symptomatic hepatotoxicity (abnormal liver function test results) for patients on fezolinetant (paragraph 7.9, fezolinetant PSD March 2025 PBAC meeting).

6.31 The resubmission maintained a claim of manageable safety of fezolinetant compared to placebo. The evaluation and the ESC considered that although the incidence of AEs was generally similar between fezolinetant and placebo at Week 52, given the PBAC's previous concerns regarding the risk of hepatoxicity associated with fezolinetant and the lack of longer-term safety data, a claim of inferior safety remained more appropriate.

6.32 The PBAC considered that the claim of superior comparative effectiveness compared to no treatment, for the revised population of patients proposed in the pre-PBAC response who are contraindicated to MHT or who have ceased due to side-effects or lack of efficacy, was reasonable.

6.33 The PBAC recalled that it previously considered that the claim of manageable non-inferior comparative safety was not adequately supported by the data, given the risks of hepatotoxicity associated with fezolinetant and lack of long-term data (paragraphs 6.38, fezolinetant PSD, March 2025 PBAC Meeting). The PBAC maintained this view, considering that fezolinetant has inferior safety compared to no treatment.

Economic analysis

6.34 Compared to the March 2025 submission, the cost-utility analysis in the resubmission was largely unchanged, and the model structure was retained.

6.35 A summary of the PBAC's main concerns and key changes in the resubmission is presented in Table 8.

Table 8: Summary of key changes to the cost-utility analysis

Component	March 2025 submission; ESC and PBAC comments	November 2025 resubmission	Impact of change
Drug cost	Proposed AEMP=$[redacted]/pack (DPMQ=$[redacted]). The PBAC considered that the price would need to be substantially reduced to realise an ICER in the range of $[redacted][2] to $[redacted][3] per QALY, which the PBAC considered would be more acceptable in the context of the uncertain benefit (para 7.11, fezolinetant, PBAC MIN, March 2025 PBAC meeting).	Proposed effective AEMP=$[redacted]/pack (effective DPMQ= $[redacted]).	The price reduction and inclusion of compliance rate in the resubmission led to a [redacted]% decrease in the ICER, from $[redacted][1] in the March 2025 base case to $[redacted][2] per QALY gained in this resubmission. This increased slightly to $[redacted][2] per QALY gained after incorporating the costs of LFTs. The DPMQ remained higher than the private market price. The ESC noted that application of a compliance rate was less conservative than the previous submission.
Compliance rate	Assumed to be 100%.	Changed to 77.9% based on real-world evidence.	
Health state costs, LFT	No consideration of LFT cost. The PBAC noted the increasing safety signals internationally concerning drug induced liver disease with the use of fezolinetant and indicated that the cost of LFT was inappropriately excluded (para 6.39, fezolinetant, PBAC MIN, March 2025 PBAC meeting).	LFT frequency and cost included. Costs in 2023-2024 values.	In the resubmission, LFT costs were included for all patients receiving fezolinetant at baseline, and at 1, 2, 3, 6, and 9 months, in accordance with FDA and EMA labelling requirements. LFTs from the second year onwards were not included in the economic model, which may be inappropriate. The revised PI presented by the resubmission recommended monthly evaluation for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement (para 4.4, fezolinetant PI). Incorporating the cost of one annual LFT follow-up from year two increased the ICER by [redacted]% (see Table 16). The ESC considered this was appropriate but noted the change made minimal difference to the ICER.

Source: Table "summary of key changes in the model", p67 of the resubmission and compiled during the evaluation.
AEMP=Approved Ex Manufacturer Price, DCE=discrete choice experiment; ICER=incremental cost-effectiveness ratio; LFT=liver function test; MIN=minutes; QALY=quality-adjusted life year; VMS=vasomotor symptoms.
Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$15,000 to < $25,000*
[3] *$25,000 to < $35,000*

6.36 For clarity, the stepped changes from the March 2025 submission to the November 2025 resubmission, along with their impact on the base case ICER, are summarised in Table 9. Compared to the March 2025 submission, changes made in the resubmission reduced the ICER by [redacted]%.

Table 9: Model changes (versus March 2025) and the stepped effect of each amendment on the ICER

	Parameter change	Incr. Cost	Incr. QALYs	ICER	% Change
March 2025 submission base case	Presented by the sponsor	$ [redacted]	0.091	$ [redacted] [1]	N/A
November 2025 resubmission base case	+ Change in drug cost	$ [redacted]	0.091	$ [redacted] [2]	- [redacted] %
	+ Change in compliance rate	$ [redacted]	0.091	$ [redacted] [3]	- [redacted] %
	+ Addition of LFT costs	$ [redacted]	0.091	$ [redacted] [a3]	- [redacted] %
	Presented by the sponsor	**$ [redacted]**	**0.091**	**$ [redacted] [3]**	**- [redacted] %**

Source: compiled during the evaluation.
ICER=incremental cost-effectiveness ratio; Incr=incremental, LFT=liver function test; QALY=quality adjusted life years.
[a] A minor discrepancy (0.006%), attributable to a small difference in incremental costs, was observed between the ICER estimated from the reported parameter changes and the ICER stated in the resubmission, with the underlying cause of this variation remaining unclear.
Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$25,000 to < $35,000*
[3] *$15,000 to < $25,000*

6.37 All other model assumptions and inputs were the same as presented in the March 2025 submission and the pre-PBAC response, including the model structure, time horizon, transition probabilities and utility values. A summary of the key components of the economic evaluation is presented in Table 10.

Table 10: Summary of model structure, key inputs and rationale

Component	March 2025 submission	Justification/comments
Treatment	Fezolinetant vs no treatment	This was appropriate.
Population	Included post-menopausal women with moderate to severe VMS for whom MHT is unsuitable.	Efficacy and utility inputs in the economic model used outcomes for the ITT population. The change from baseline in the mean frequency of moderate to severe VMS in the MHT-suitable population (excluding MHT-averse individuals) in DAYLIGHT was generally consistent with that observed in the ITT population (see Table 5), and the evaluation considered this assumption was reasonable.
Type of analysis	Cost-utility analysis	This was appropriate.
Mean age	54.5 years, from DAYLIGHT	This was appropriate.
VMS frequency distribution at baseline	Source: DAYLIGHT. • 0 ≤ VMS frequency < 2: 0% • 2≤ VMS frequency <7: 0.2% • 7≤ VMS frequency <9: 41.8% • VMS frequency ≥9: 57.9%	This was appropriate.
Outcomes	LYG, QALYs	This was appropriate.
Time horizon	10 years	Time horizon remained one of the key drivers of the model. The PSCR argued that incorporating the probabilities of VMS cessation and treatment discontinuation moderated the assumption of persistent efficacy, yielding a mean treatment duration of 2.88 years over a ten-year time horizon. However, the ESC considered that cessation of VMS symptoms and discontinuation of treatment is part of the natural history, but does not directly address uncertainty related to the assumed sustained treatment effect from weeks 20–24 over a 10-year period for patients remaining on treatment. The ESC maintained that a 5 year time horizon would be more appropriate. Treatment effects in the model were extrapolated from 24 weeks (DAYLIGHT) to 10 years, assuming sustained benefit for the duration of treatment.
Methods used to generate results	Markov model approach	This approach was reasonable.

Health states	• 0 ≤ VMS frequency < 2 • 2≤ VMS frequency <7 • 7≤ VMS frequency <9 • VMS frequency ≥9 • Natural cessation of VMS • Death	The ESC previously raised concerns about the model structure, as it overlooked VMS severity, showed minimal utility differences between groups, and lacked validation through alternative approaches. It also contradicted the DCE findings (para 6.42-6.47, fezolinetant PSD March 2025). The resubmission provided further justifications to support the model structure, regarding the exclusion of VMS severity and the use of two separate VMS frequency health states ('2≤VMS frequency<7' and '7≤VMS frequency<9'), when there was no significant utility difference. However, the results of the submission's correlation analysis between VMS frequency and severity indicated low to moderate correlation between severity and frequency (correlation coefficients 0.236 to 0.477). The PSCR argued that the model's focus on VMS frequency rather than severity was due to the objectivity of frequency as a measure and the lack of standardised scales for clinician-reported severity. It noted that excluding severity was unlikely to introduce bias in favour of fezolinetant, given the significantly greater reduction in severity compared with placebo, and that severity was still captured indirectly through utility measures.
Cycle length	Four weeks, half cycle correction	This was appropriate.
Utility values	Mean utility values from DAYLIGHT (EQ-5D-5L mapped to UK EQ-5D-3L): • 0 ≤ VMS frequency < 2= 0.833 • 2≤ VMS frequency <7= 0.793 • 7≤ VMS frequency <9= 0.785 • VMS frequency ≥9= 0.747 • Natural cessation of VMS= 0.843 Other health state utilities were based on Whiteley et al., 2013, and clinician estimates.	The ESC previously considered that it would be useful to see the Australian value set applied directly to the 5L data in the sensitivity analyses, although it is unlikely to have a substantial impact on the ICER (para 6.51, fezolinetant PSD March 2025). The resubmission argued that applying the Australian value set for estimating health state utility values was unlikely to have a substantial impact on model results; therefore, the health state utility values remain unchanged. The ESC considered that the Australian value sets should have been presented consistent with the PBAC guidelines (v5.0).
Efficacy data sources	Primary: DAYLIGHT, Secondary: DAYLIGHT + SKYLIGHT 1 & 2	This was appropriate.
Discontinuation	• 0-24 weeks: DAYLIGHT 0-24 • 24+ weeks: DAYLIGHT 0-24 for no treatment and SKYLIGHT 1 &2 (MHT unsuitable, week 24-52) for fezolinetant.	The ESC previously considered that the assumption that treatment discontinuation is lower in the fezolinetant arm may be reasonable, however the current model appeared to double-count return to baseline in the no treatment arm, hence biasing the ICER in favour of fezolinetant. The ESC noted the possibility of modelling trial discontinuation based on event frequency, and then to apply those rates to both arms equally (para 6.57, fezolinetant PSD March 2025). This was not addressed by the resubmission. Additionally, discontinuation defined in DAYLIGHT (due to lack of efficacy, MHT-related side effects, advised by healthcare provider to stop due to length of time on MHT or due to age ≥ 60 years) was different to that in SKYLIGHT1&2 (due to medical concerns), raising further concerns about the accuracy of using the SKYLIGHT-reported discontinuation rate for the fezolinetant arm from Week 24 onwards.
VMS cessation	Median duration of symptoms= 7.4 years (source: Avis et al., 2015)	This was appropriate.
Treatment costs	AEMP=$[redacted]/pack.	The AEMP was decreased by [redacted]% to AEMP=$[redacted]/pack in the resubmission.

Compliance rate	Assumed to be 100%	The resubmission included a compliance rate of 77.9%, based on real-world data. This was estimated using the utilisation and compliance data for fezolinetant from 10 countries where the treatment was available, including Australia (Attachment 16 of the resubmission). The real-world compliance rate was higher than the DAYLIGHT study's ≥168-day exposure rate (68.1%, para 5.6, DAYLIGHT CSR).
Health state costs	No consideration of LFT. Costs were based on 2022-2023.	The resubmission included LFT costs for all patients receiving fezolinetant at baseline, and at 1, 2, 3, 6, and 9 months, in accordance with FDA and EMA labelling requirements. This was appropriate.
Discounting	5% (costs and QALYs)	Appropriate.
Software	Excel 2016	Appropriate.

Source: Table 3.1-1, p68 of the resubmission, and compiled during the evaluation.
AEMP=Approved Ex Manufacturer Price, LFT=liver function test; LYG=life-years gained; MHT=menopausal hormone therapy, Nov.=November; QALY= quality-adjusted life-years; VMS=vasomotor symptoms.
Blue shading indicates data previously seen by the PBAC.

6.38 The updated literature review conducted by the sponsor did not identify any new studies. An independent search conducted during the evaluation identified the NICE draft guideline on fezolinetant for treating VMS associated with menopause. The guideline was marked as 'in progress' and indicated that the treatment was 'not recommended,' pending the company's response to the draft. The reason for this recommendation was stated as: 'This is because there is not enough evidence to determine whether fezolinetant is value for money'. The NICE draft guideline indicated that:

- 'Using a structure based solely on frequency does not capture the impact on severity. Clinical advice was that using frequency as a proxy for severity was a concern and not usual NHS practice. The external assessment group (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 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 should be noted that this was not consistent with the sponsor's DCE (para 6.9), which indicated that improvement in VMS severity was a less important factor for performance compared to VMS frequency.

The NICE draft guideline 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' (para 3.10, pp14-15, NICE Draft Guideline, March 2025) [11].

6.39 The structure and approach of the economic evaluation, consisting of a Markov cohort based on the average daily frequency of VMS events, remained unchanged from the March 2025 submission. The discrete health states (i.e., VMS<2, 2≤VMS<7, 7≤VMS<9, and VMS≥9) were determined based on a post hoc analysis of DAYLIGHT to group VMS frequencies by EQ-5D utility values. The ESC previously noted that there was a clear drop in mean utility at 9 daily VMS episodes, which suggested this cut point was reasonable, however, the other utility categories appeared somewhat arbitrary. The ESC previously noted that it was not possible to test the effect of using different threshold categories in the model (paragraph 6.45, fezolinetant PSD March 2025 PBAC meeting). The resubmission did not present alternative analyses, such as latent class analysis, to validate the final VMS frequency groupings.

6.40 VMS severity was not considered when determining the health states. The ESC previously advised that use of VMS frequency alone was likely to be reasonable as frequency is a more objective measure, is likely to be correlated with severity, and including both severity and frequency in the model would likely result in substantial double-counting of the benefit (paragraph 6.47, fezolinetant PSD March 2025 PBAC meeting). The resubmission indicated that the exclusion of VMS severity from the model was a deliberate decision based on the lack of standardised, objective measures, with frequency chosen instead as a more reliable and widely reported endpoint. The resubmission reported a series of correlation analyses between VMS frequency and severity, demonstrating the correlation between VMS frequency and severity (see Table 11 and Table 12), and argued that incorporating severity alongside frequency could result in double counting treatment effects. These analyses were also reported in the March 2025 pre-PBAC response.

Table 11: Patient: Correlation coefficients between VMS frequency and severity for the Fezolinetant 45 mg

Trial	Timepoint	N	Correlation coefficients
SKYLIGHT 1	Week 4	164	0.467
	Week 12	146	0.408
SKYLIGHT 2	Week 4	155	0.472
	Week 12	145	0.236
Pooled SKYLIGHT 1 and 2	Week 4	319	0.477
	Week 12	291	0.310

Source: Figure 3.2-3, p75 of the resubmission
VMS=vasomotor symptoms.
Blue shading indicates data previously seen by the PBAC.

[11] NICE 2025. Fezolinetant for treating vasomotor symptoms associated with the menopause [ID5071]. Accessed on 14/07/2025: https://www.nice.org.uk/consultations/2918/1/recommendations#recommendations.

Table 12: Association between mean moderate and severe VMS frequency per 24h and PGI-C VMS for fezolinetant 45 mg and placebo (Full Analysis Set)

Mean VMS frequency per 24h	PGI-C VMS, n (%)						
	Much Better	Moderately Better	A little better	No change	A little worse	Moderately worse	Much worse
DAYLIGHT							
<2	448 (30.7)	81 (5.6)	27 (1.9)	6 (0.4)	0	0	1 (0.1)
≥2 to <7	176 (12.1)	133 (9.1)	137 (9.4)	127 (8.7)	11 (0.8)	10 (0.7)	4 (0.3)
≥7 to 9	12 (0.8)	19 (9.1)	23 (1.6)	68 (4.7)	6 (0.4)	3 (0.2)	5 (0.3)
≥9	5 (0.3)	12 (0.8)	32 (2.2)	89 (6.1)	8 (0.5)	8 (0.5)	7 (0.5)
Pooled SKYLIGHT 1 and SKYLIGHT 2 (MHT unsuitable subpopulation, up to Week 12) and DAYLIGHT							
<2	634 (25.9)	122 (5.0)	43 (1.8)	10 (0.4)	3 (0.1)	1 (0.0)	1 (0.0)
≥2 to <7	293 (12.0)	231 (9.4)	247 (10.1)	176 (7.2)	15 (0.6)	13 (0.5)	7 (0.3)
≥7 to 9	23 (0.9)	37 (1.5)	67 (2.7)	119 (4.9)	9 (0.4)	4 (0.2)	8 (0.3)
≥9	20 (0.8)	37 (1.5)	104 (4.2)	178 (7.3)	18 (0.7)	16 (0.7)	12 (0.5)
Pooled SKYLIGHT 1 and SKYLIGHT 2 (MHT unsuitable subpopulation, up to Week 52 for fezolinetant patients and up to Week 12 for placebo patients) and DAYLIGHT							
<2	761 (27.5)	148 (5.3)	51 (1.8)	12 (0.4)	5 (0.2)	1 (0.0)	1 (0.0)
≥2 to <7	335 (12.1)	262 (9.5)	275 (9.9)	181 (6.5)	16 (0.6)	16 (0.6)	9 (0.3)
≥7 to 9	25 (0.9)	40 (1.4)	72 (2.6)	120 (4.3)	9 (0.3)	4 (0.1)	8 (0.3)
≥9	25 (0.9)	50 (1.8)	113 (4.1)	181 (6.5)	18 (0.7)	16 (0.6)	13 (0.5)

Source: Figure 3.2-4, p75 of the resubmission

MHT=menopausal hormone therapy, PGI-C=Patient Global Impression of Change; VMS=vasomotor symptoms.

Note: Each cell represents the number of visits at which a particular PGI-C VMS response and a particular mean frequency of moderate to severe VMS occurs. Only data from the placebo and fezolinetant 45mg are included in this analysis. Each patient contributed all the visits for which they had both endpoints recorded.

Blue shading indicates data previously seen by the PBAC.

6.41 The results indicated low to moderate correlation between severity and frequency (correlation coefficients 0.236 to 0.477). The presented information on association between mean moderate and severe VMS frequency per 24-hour and Patient Global Impression of Change (PGI-C) VMS for fezolinetant and placebo was difficult to interpret as there were more patients reporting an improvement versus worsening on PGI-C for each VMS frequency category.

6.42 The model used four-weekly transition probability matrices up to Week 24, derived from DAYLIGHT (Weeks 0–24). Beyond Week 24, data from Weeks 20–24 of DAYLIGHT were assumed constant and carried forward until model end (or until treatment discontinuation). The resubmission indicated that the transition probabilities remained similar to the March 2025 submission for both the intervention and comparator. The resubmission further noted that although the proposed revised population excludes the MHT-averse subgroup, it is a subgroup of the majority of trial patients and has similar outcomes to the ITT population. Hence, the efficacy and utility inputs for the economic model were still applicable and were unchanged. The resubmission reported the change from baseline in VMS frequency and severity at Week 24 for the DAYLIGHT post hoc MHT unsuitable (excluding MHT averse) population, which the evaluation considered was generally consistent with the overall DAYLIGHT MHT-unsuitable population (see Table 5 and Table 6). The ESC considered this was reasonable.

6.43 The resubmission's model continued to assume sustained treatment effect over 10 years despite no data beyond 52 weeks. The pre-PBAC response contented that the

modelled sustained symptom reduction has been demonstrated through 52 weeks in the pooled SKYLIGHT-1 and -2 trials, with no evidence of waning efficacy or emergent tolerance. The pre-PBAC response also noted that despite the 10 year model horizon median treatment duration in the model is only 28.5 months and only 12.5% of patients are still on fezolinetant treatment by 7.5 years.

6.44 For women discontinuing fezolinetant and no treatment at any point, the model assumed they would lose all treatment benefits and return to their baseline VMS values, with potential natural cessation of VMS. The ESC previously noted that treatment discontinuation rates were sourced differently for fezolinetant (DAYLIGHT and SKYLIGHT1&2) and the no treatment arm (DAYLIGHT), with the latter potentially double-counting return to baseline due to higher symptom recurrence and discontinuation. This may bias the ICER in favour of fezolinetant (paragraph 6.57, fezolinetant PSD March 2025 PBAC meeting). This remained unaddressed in the resubmission. The PSCR argued that discontinuation rates were appropriately derived from clinical trials, with health state frequencies and discontinuation carried forward from the RCT. The ESC considered it would be more appropriate to set the fezolinetant discontinuation rate for the entire model equal to the week 0-24 discontinuation rate from DAYLIGHT (i.e., 2.4%). The Pre-PBAC response maintained that "For fezolinetant, long-term trial follow-up (from SKYLIGHT trials) indicates a stable, low discontinuation rate (fezolinetant approx. 1.32% per cycle), which is carried forward because the patients remaining are likely responders. The model conservatively keeps the placebo discontinuation rate unchanged from the initial trial period, although the placebo effect is likely to diminish over time and therefore increase real-world discontinuation in patients receiving no treatment."

6.45 The PSCR noted that, given the artificial nature of placebo, the effectiveness of the no-treatment arm was likely overestimated, while discontinuation was likely underestimated. The ESC considered, given the placebo effect observed in the trial was likely in part due to regression to the mean, a more conservative assumption would have been to assume that the no treatment arm in the trial represented the natural history of the disease and the incremental benefit of fezolinetant be restricted to the incremental difference observed between the two arms in the trial (i.e., excluding additional benefit from returning patients to baseline VMS frequency post discontinuation).

6.46 The ESC noted that the previous submission applied a compliance rate of 100% in calculation of drug costs whereas the resubmission included a compliance rate of 77.9%. Compared to the previous submission model, the application of a compliance rate only affects costs (i.e., reduces costs for fezolinetant) whereas outcomes in the resubmission model were unchanged from the previous model. The compliance rate was based on real-world utilisation and compliance data for fezolinetant from 10 countries where the treatment was available, including Australia (Attachment 16 of the resubmission). In Australia, the compliance rate was 73% over 12 months on the market, while the average across the 10 countries was 77.9% over an average observation period of 13 months. The evaluation considered that applying the compliance rate from the real-world study, which may already reflect some degree of

discontinuation, may risk double counting, introducing uncertainty. The ESC noted that it was unclear from the real-world data (Attachment 16 of the submission) whether the compliance rates reported also captured discontinuation, in which case it would not be appropriate to apply both discontinuation and compliance rates. However, the ESC noted the compliance rate was consistent with additional data presented in figure 1 of the PSCR (which reflected adherence based on medication possession ratio). In addition, the real-world compliance rate was higher than the DAYLIGHT study's ≥168-day exposure rate (68.1%, para 5.6, DAYLIGHT CSR). Use of the higher compliance rate from the real-world data for calculation of drug costs, without adjustment of the trial outcomes, would therefore be a conservative approach and the ESC considered this may be reasonable. The pre-PBAC response considered that use of the 100% compliance rate in the original submission was overly conservative.

6.47 Table 13 summarises health care resource use and costs in the economic evaluation. The effective AEMP of fezolinetant was $[redacted], resulting in a DPMQ of $[redacted] for a pack of 30 × 45mg tablets of fezolinetant. The AEMP proposed in the resubmission was [redacted]% lower than that proposed in the March 2025 submission.

Table 13: Health care resource items and unit costs included in the economic evaluation

Resource item	Unit cost	Source of unit cost	Usage in the economic evaluation	
			Fezolinetant	No treatment
Medicines				
Fezolinetant (45mg/day)	$[redacted]	Requested price	$[redacted] per 28-day cycle	$0.00
Medical services [a]				
Physician visits (first visit)	$82.90	MBS code 36	Once (as one-off), in all health states with VMS.	
Physician visits (follow-up visit)	$42.85	MBS code 23	Twice per year, in 2≤VMS<7, and four times per year in 7≤VMS<9 & VMS≥9 health states.	
Specialist visit (first visit)	$98.95	MBS code 104	Once (as one-off), in VMS≥9 health state.	
Specialist visit (follow-up visit)	$49.75	MBS code 105	Not included in the base case.	
Liver function test	$17.7	MBS code 66512	Administered at baseline, 1, 2, 3, 6 and 9 months. [b]	

Source: Table 3.6-1, p89, Table 3.6-2, p90, Table 3.6-5, p90 and Table 3.6-6, p90 of the resubmission.
VMS=vasomotor symptoms

[a] Healthcare resource use costs were applied per cycle, converted from annual costs. No treatment or resource use costs were applied to the "cessation of VMS" health state.

[b] LFTs from the second year onwards were not included in the economic model, which may be inappropriate. The revised Australian PI, presented by the resubmission, indicates follow-up evaluation of hepatic function is recommended monthly for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement (para 4.4, fezolinetant PI). The Australian PI (July 2024) indicates a baseline and subsequent periodic follow-up evaluation of hepatic function (at least once within the first 3 months of treatment).

Blue shading indicates data previously seen by the PBAC.

6.48 The resubmission reported that, according to PBAC advice (paragraph 6.49, fezolinetant PSD March 2025 PBAC meeting), an additional LFT was recommended for all patients receiving fezolinetant. In line with the revised PI, LFTs should be conducted at baseline and at 1, 2, 3, 6, and 9 months and thereafter periodically based on clinical judgement.

6.49 The model included an option to account for indirect costs, including productivity loss and travel expenses as a sensitivity analysis. Productivity loss-related costs and travel expenses remained unchanged from the March 2025 submission. These costs were appropriately excluded in the base case.

6.50 A summary of the key drivers of the model is presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact (Base case: $[redacted][1]/QALY gained)
Model structure	Model structure was based on VMS frequency. The final four health states adopted in the submission may not be entirely appropriate, given that mean utilities did not significantly differ between patients with '2≤ VMS frequency <7' and '7 ≤VMS frequency <9' based on DAYLIGHT. Additionally, VMS severity was not considered when determining the health states. The submission also failed to present any alternative analyses, such as latent class analysis, to validate the final VMS frequency groupings. Furthermore, the chosen model structure deviated from the submission's DCE results, which indicated that patients place greater value on a 50% relative reduction in VMS frequency. The model's structural assumptions are likely very impactful on the ICER but cannot be tested in sensitivity analysis.	Unclear, can't be tested.
Time horizon	Base case time horizon was 10 years. Data were, however, only available for up to 24 weeks in DAYLIGHT. Beyond 24 weeks, treatment effects in the model were extrapolated based on the assumption of maintaining the same benefit whilst on treatment.	High, favours fezolinetant. Reducing the time horizon to 5 years increased the ICER by [redacted]% to $[redacted][2] per QALY gained.
Treatment discontinuation	Discontinuation was sourced from DAYLIGHT and SKYLIGHT 1 and 2 for fezolinetant, and from DAYLIGHT for the no treatment arm. At discontinuation, the model assumed that the patient returns to baseline event frequency. The ESC previously noted that the model may have double-counted discontinuation in the no treatment arm by assuming both a higher likelihood of symptom worsening and a higher discontinuation rate leading to a return to baseline, potentially biasing the results in favour of fezolinetant. The ESC recommended modelling discontinuation based on event frequency and applying it equally (para 6.57, fezolinetant PSD March 2025). This was not addressed by the resubmission.	High, favours fezolinetant. The impact was not tested by the resubmission. The impact remained unclear.
Compliance rate	The base-case compliance rate from a real-world study was 77.9%, higher than the DAYLIGHT study's ≥168-day exposure rate of 68.1% (para 5.6, DAYLIGHT CSR). However application of a compliance rate was less conservative that the previous submission.	Unclear. Adjusting this to the compliance rate observed in DAYLIGHT results in a [redacted]% decrease in the ICER. Additionally, assuming a 100% compliance rate increases the ICER by [redacted]%.

Source: compiled during the evaluation.
CSR=clinical study report; DCE= discrete choice experiment, VMS=vasomotor symptoms, ICER=incremental cost-effectiveness ratio, QALYs=quality-adjusted life-year.
Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *$15,000 to < $25,000*
[2] *$25,000 to < $35,000*

6.51 A summary of the stepped economic analyses is presented in Table 15. The estimated base case ICER for the proposed scenario (fezolinetant) versus the current scenario (no treatment) was $15,000 to < $25,000 per QALY gained.

Table 15: Results of the stepped economic evaluation

	March 2025 submission			Resubmission		
Step and component	**Fezolinetant**	**No treatment**	**Increment**	**Fezolinetant**	**No treatment**	**Increment**
Step 1: Trial-based analysis, 24 weeks data from the DAYLIGHT trial (costs=drug costs, outcome=VMS frequency)						
Costs: drug acquisition	$[redacted]	$0.00	$[redacted]	$[redacted]	$0	$[redacted]
Outcome: patient proportion in VMS<7 state (mild)	66.18%	51.04%	15.14%	66%	51%	15.6%
Incremental cost per extra 'patients in the mild state' gained			$[redacted] [1]			$[redacted] [1]
Step 2: Trial-based analysis, 24 weeks data from the DAYLIGHT trial (costs=drug costs + resource utilisation, outcome=VMS frequency)						
Costs: drug acquisition + resource use	$[redacted]	$150	$[redacted]	$[redacted]	$151	$[redacted]
Outcome: patient proportion in VMS<7 state (mild)	66.18%	51.04%	15.14%	66%	51%	15.6%
Incremental cost per extra 'patients in the mild state' gained			$[redacted] [1]			$[redacted] [1]
Step 3: Trial-based analysis from Step 2, adding QALYs based on utility estimate by VMS frequency						
Costs: drug acquisition + resource use	$[redacted]	$150	$[redacted]	$[redacted]	$151	$[redacted]
Outcome: QALYs	0.368	0.362	0.006	0.368	0.362	0.006
Incremental cost/extra QALYs gained			$[redacted] [2]			$[redacted] [3]
Step 4: Model-based analysis with 10-year time horizon, discounting of costs and outcomes						
Costs: drug acquisition + resource use	$[redacted]	$896	$[redacted]	$[redacted]	$896	$[redacted]
Outcome: QALYs	6.278	6.187	0.091	6.277	6.185	0.091
Incremental cost/extra QALY gained (base case)			**$[redacted]** [4]			**$[redacted]** [5]

Source: Para 6.60, fezolinetant, PBAC MIN, March 2025 and Table 3.9.1, p96 of the resubmission.
VMS=vasomotor symptoms, QALYs=quality-adjusted life-years.
Blue shading indicates data previously seen by the PBAC
The redacted values correspond to the following ranges:
[1] *$0 to < $5,000*
[2] *$95,000 to < $115,000*
[3] *$55,000 to < $75,000*
[4] *$35,000 to < $45,000*
[5] *$15,000 to < $25,000*

6.52 The evaluation and the ESC considered that as with the March 2025 submission, the resubmission's base case ICER may be uncertain because of uncertain assumptions in the model structure, application of different sources of discontinuation rates, and extrapolation of the treatment effect beyond the trial.

6.53 The disaggregated results from the resubmission showed the model was driven by drug costs (i.e., 91% of the total incremental costs) and fezolinetant treated patients spending more time in the lower VMS frequency health states compared to those in the no treatment arm. QALYs and life years gained remained unchanged from the March 2025 submission.

6.54 The results of key sensitivity analyses are summarised in Table 16. The ICER was most sensitive to inputs relating to time horizon, treatment discontinuation, treatment compliance rate, and utility estimates. The evaluation and the ESC considered that structural assumptions within the model were likely the predominant drivers of ICER uncertainty; however, these assumptions are inherently non-parametric and cannot be tested through sensitivity analyses.

Table 16: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% Change in ICER
Base case (resubmission)	**$** [redacted]	**0.09**	**$** [redacted][1]	**base**
March 2025 submission base case	$ [redacted]	0.09	$ [redacted][2]	-
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes	$ [redacted]	0.11	$ [redacted][1]	- [redacted]%
• 3.5% costs and outcomes	$ [redacted]	0.10	$ [redacted][1]	- [redacted]%
Time horizon (base case 10 years)				
• 5 years	$ [redacted]	0.07	$ [redacted][3]	+ [redacted]%
• 7 years	$ [redacted]	0.08	$ [redacted][1]	+ [redacted]%
Starting age (base case: 54.5 years, DAYLIGHT)				
• Median age of menopause onset in Australia: 51.0 years	$ [redacted]	0.09	$ [redacted][1]	- [redacted]%
Utility (base case: source: DAYLIGHT, VMS frequency 2 to <7: 0.793 and 7 to <9: 0.785, p<0.05)				
• Source: Whiteley et al., 2013	$ [redacted]	0.09	$ [redacted][1]	+ [redacted]%
• Source: UK clinical estimates	$ [redacted]	0.12	$ [redacted][1]	- [redacted]%
• Similar value for health state 2 ≤ VMS-F < 7 and 7 ≤ VMS-F < 9; State 2 = State 3	$ [redacted]	0.09	$ [redacted][1]	+ [redacted]%
• Similar value for health state 2 ≤ VMS-F < 7 and 7 ≤ VMS-F < 9; State 3 = State 2	$ [redacted]	0.09	$ [redacted][1]	+ [redacted]%
Efficacy (base case: all arms from Week 24+, will use DAYLIGHT 20-24 values per cycle				
• Use of DAYLIGHT 0-24 average after w 24+	$ [redacted]	0.09	$ [redacted][1]	- [redacted]%
Discontinuation (base case: Weeks 0–24 from DAYLIGHT for both fezolinetant and no treatment (4-weekly probability: 4.43% and 4.17%, respectively); Week 24+ from SKYLIGHT for fezolinetant (1.32%), with no treatment set to 100%				
• For fezolinetant, setting the discontinuation rate for Weeks 0-24 and Weeks 24+ (ie entire model) equal to the Week 0-24 rate from DAYLIGHT (2.4%)	$ [redacted]	0.05	$ [redacted][3]	[redacted]%
• For fezolinetant, setting the discontinuation rate for Weeks 0-24 and Weeks 24+ (ie entire model) equal to the Week 24+ rate from SKYLIGHT (1.3%)	$ [redacted]	0.10	$ [redacted][1]	- [redacted]%
VMS cessation (bae case: Avis et al., 2015)				
• Politi et al., 2008	$ [redacted]	0.07	$ [redacted][3]	+ [redacted]%
• Mid-point between Avis et al. & Politi et al.	$ [redacted]	0.08	$ [redacted][1]	+ [redacted]%
Perspective (base case: payer)				
• Societal	-$ [redacted]	0.09	Dominant	Dominant
LFT (base case: included at baseline, and at 1, 2, 3, 6, and 9 months on the first year of treatment)				
• Exclusion of LFT	$ [redacted]	0.09	$ [redacted][1]	- [redacted]%
• Inclusion of one LFT from year two onwards	$ [redacted]	0.09	$ [redacted][1]	+ [redacted]%
Compliance rate (Base case: 77.9%)				
• Based on DAYLIGHT: 68.1%	$ [redacted]	0.09	$ [redacted][1]	- [redacted]%
• Real-world data in Australia: 73.0%	$ [redacted]	0.09	$ [redacted][1]	- [redacted]%
• March 2025 base case: 100%	$ [redacted]	0.09	$ [redacted][3]	+ [redacted]%
Multivariate sensitivity analysis				
1 - Time horizon to 5 years (base case 10 years)	$ [redacted]	0.07	$ [redacted][3]	+ [redacted]%
2 - #1 + For fezolinetant, setting the discontinuation rate for Weeks 0-24 and Weeks 24+ (ie entire model) equal to the Week 0-24 rate from DAYLIGHT (2.4%)	$ [redacted]	0.05	$ [redacted][3]	+ [redacted]%
3 - #2 + Compliance rate= 100%	$ [redacted]	0.05	$ [redacted][2]	+ [redacted]%

Source: Table 3.10-3, p100 of the resubmission and compiled during the evaluation.
ICER=incremental cost-effectiveness ration, LFT=liver function test; QALYs=Quality adjusted life-years, VMS=vasomotor symptoms.
Blue shading indicates data previously seen by the PBAC. Italics indicate results calculated for the ESC advice.
The redacted values correspond to the following ranges:

[1] *$15,000 to < $25,000*
[2] *$35,000 to < $45,000*
[3] *$25,000 to < $35,000*

6.55 The ESC considered that a multivariate sensitivity analysis including a 5 year time horizon and fezolinetant discontinuation rate for the entire model set to the Week 0-24 rate from DAYLIGHT (2.4%) would address some of the PBAC's previous major concerns regarding the inputs to the economic evaluation (though uncertainty regarding outcomes due to the model structure remains). This analysis resulted in a 40% increase in the ICER, to $25,000 to < $35,000 per QALY gained. However, the pre-PBAC response maintained the view that the time horizon and discontinuation rate applied in the model's base case were appropriate.

6.56 The PBAC noted that the updated PI recommended LFTs at 1, 2, 3, 6, and 9 months on the first year of treatment (which was included in the resubmission model) and also thereafter periodically based on clinical judgement (which was not included in the resubmission model). The PBAC considered that it would be reasonable to assume that patients would require an additional LFT annually and that these costs should be accounted for in the model. The PBAC noted that inclusion of one LFT from year 2 onwards increased the ICER to $25,000 to < $35,000 per QALY gained. When this cost was added to the multivariate sensitivity analysis described in paragraph 6.55, the ICER increased to $25,000 to < $35,000 per QALY gained.

Cost/patient/year

Table 17: Drug cost per patient for fezolinetant

	Trial	Economic Model		Financial Estimates	
	DAYLIGHT	March 2025	Resubmission	March 2025	Resubmission
Mean dose	45 mg/day	45 mg/day	45 mg/day	45 mg/day	45 mg/day
Mean treatment duration	157.4 days (5.2 months) [a]	1,053.3 days (34.6 months) [b]	1,053.3 days (34.6 months) [b]	NR	256.3 days [c] (8.4 months) Per year
Median treatment duration	168.0 days (5.5 months) [a]	866.9 days (28.5 months)	866.9 days (28.5 months)	NR	NR
Pack cost (×30 tablets)	NR	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Unit cost	NR	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Compliance rate	68.1% [d]	100%	77.9% [e]	72.6% [f]	77.9% [e]
Cost/patient/month	NR	$[redacted] [g]	$[redacted] [g]	$[redacted] [h]	$[redacted] [i]
Cost/patient/year	NR	$[redacted] [j]	$[redacted] [j]	$[redacted] [k]	$[redacted] [l, m]

Source: compiled during the evaluation

NR=not reported; resub=resubmission; sub=submission.

[a] Mean treatment duration was 144.3 and 157.4 days in no treatment and fezolinetant arms, respectively. Median treatment duration was 168.0 days in both arms (Table 9.2.1.1.1, DAYLIGHT CSR). The median trial duration was 24 weeks plus three weeks safety follow-up.

[b] This was captured from the economic model (Attachment 12 of the submission, CEA, 'Fezolinetant Trace' worksheet, Cell BB85).

[c] This was estimated from the discontinuation rate reported in DAYLIGHT at 24 weeks (13.72%). Annual discontinuation rate was used to estimate the average treatment duration of 265.29 days (=365.25 days*(1-27.4%)). The resubmission's approach to calculate the annual discontinuation rate from the 24-week rate may be subject to some uncertainty, as discussed in Table 19.

[d] The proportion of patients with at least 24 weeks of treatment were 68.1% for fezolinetant 45 mg and 65.5% for placebo (Table 9, p29 of DAYLIGHT CSR).

[e] Compliance rate of 77.9% was estimated using the utilisation and compliance data for fezolinetant from 10 countries where the treatment was available, including Australia. In Australia, the compliance rate was 73% over 12 months on the market, while the average across the 10 countries was 77.9% over an average observation period of 13 months.

[f] Compliance rate of 72.6% was derived from a 24-week discontinuation probability of 13.72% from the DAYLIGHT trial (Table 9.1.1.3.2, DAYLIGHT trial CSR).

[g] Calculated as: per tab cost × month length (30.42 days) × compliance rate.

[h] Calculated as 8.843 scripts per year (accounting for compliance rate) × cost/script, divided by 12 to represent monthly cost of treatment.

[i] Calculated as 9.48 scripts per year (accounting for compliance rate) × cost/script, divided by 12 to represent monthly cost of treatment.

[j] Cost per patient per month x 12.

[k] Cost per patient per year/course of treatment was calculated as 8.843 × 30-tablet scripts per year, accounting for compliance rate.

[l] This was calculated by multiplying the unit cost ($[redacted]) by the average treatment duration (256.3 days) and compliance rate (77.9%).

[m] The value presented reflects the total annual cost of treatment, adjusted for the discontinuation rate.

Blue shading indicates data previously seen by the PBAC.

6.57 The estimated cost per patient per year for fezolinetant treatment was $[redacted] in the economic model and $[redacted] per year in the financial estimates (based on a mean duration of 8.4 months per year, which included discontinuation). In the financial analysis, the estimates were applied to a prevalent patient population and the 24-week discontinuation rate from the DAYLIGHT study (13.7%) was extrapolated to an annual rate (i.e., 27.4%) and applied uniformly across any given year. In contrast, in the economic model patients were followed over time with discontinuations based on the 24-week DAYLIGHT discontinuation rate for the first 24 weeks and discontinuation rates reported in the SKYLIGHT studies for the period beyond 24 weeks (with 4-week discontinuation probabilities of 2.43% and 1.32%, respectively, which were derived using different definitions, as discussed in Table 10). Application of compliance and discontinuation rates were amended in the financial estimates provided with the PSCR and pre-PBAC response.

Estimated PBS usage & financial implications

6.58 This resubmission was not considered by DUSC. The resubmission presented updated financial estimates for the proposed listing of fezolinetant 45 mg based on the same epidemiological approach as the March 2025 submission. In summary, the main changes in the resubmission included:

- Refined patient population by excluding Australian women aged 66–79 years to align with DAYLIGHT, which excluded patients 65+, with lower rates of menopausal women with VMS symptoms.
- Added a new step to further refine fezolinetant eligibility, assuming that 60% of the eligible group (postmenopausal women with moderate to severe VMS who are unsuitable for MHT) would seek medical advice.
- Exclusion of the "MHT Averse" population consistent with the revised requested PBS restriction.
- Inclusion of discontinuation and compliance rates, replacing the earlier assumption of full-year treatment and a proxy compliance estimate.
- Reduced proposed AEMP to $[redacted] (applied DPMQ: $[redacted]), a [redacted]% decrease from the previously proposed price.
- Slightly increased uptake rates, acknowledging prior underestimation in the March 2025 submission.

6.59 A summary of the changes and effect on the net costs to PBS/RPBS are presented in Table 18.

Table 18: Financial estimate changes (versus March 2025) and the stepped effect on net costs

Financial estimates change	Net cost to PBS/RPBS (over 6 years)	% Δ vs March 2025 base case
March 2025 base case	**$[redacted][1]**	**-**
Step 1: March 2025 base case + updated the patient population using ABS 2026 data, focusing on the 40–65 age group and excluding those aged 66–79. This adjustment changed the total population from 6.2 million to 4.5 million, and updated the average rates for menopause and moderate-to-severe VMS symptoms from 65.41% and 9.80% to 52.21% and 14.89%, respectively.	$[redacted][2]	-[redacted]%
Step 2: Step 1 + Including "willingness to seek medical advice" for the MHT unsuitable patients (75% MHT unsuitable × 60% seek advice= 45.4%)	$[redacted][3]	-[redacted]%
Step 3: Step 2 + Exclusion of the "MHT Averse" population	Not applied separately	-
Step 4: Step 3 + increase in uptake rates (from [redacted]%-[redacted]% to [redacted]% to [redacted]% in years 1 to 6)	$[redacted][3]	-[redacted]%
Step 5: Update in GF patients (from [redacted] patients)	$[redacted][3]	-[redacted]%
Step 6: Step 5 + update in compliance rate (from 72.6% to 77.9%, estimated from real-world market data).	$[redacted][4]	-[redacted]%
Step 7: Step 6 + incorporating an annual discontinuation rate for prevalent patients - excluding GF patients - (265.3 days) and GF patients (182.63 days). This factor was not included in the previous model.	$[redacted][5]	-[redacted]%
Step 8: Step 7 + [redacted]% reduction in the proposed price	$[redacted][6]	-[redacted]%
Step 9: Step 8 + update on PBS/RPBS split and co-payment	$[redacted][6]	-[redacted]%
November 2025 base case (resubmission)	**$[redacted][6]**	**-[redacted]%**

Source: compiled during the evaluation from Table 4.4-2, p118 and Table 4.5-4, p121 of the resubmission and independent analysis conducted during the evaluation.
GF=grandfather; MBS=Medicare Benefits Schedule; MHT=Menopausal hormone therapy, PBS=Pharmaceutical Benefits Scheme; pop=population, RPBS=Repatriation Schedule of Pharmaceutical Benefits, VMS=vasomotor symptoms, y=year.
Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *$800 million to < $900 million*
[2] *$700 million to < $800 million*
[3] *$400 million to < $500 million*
[4] *$500 million to < $600 million*
[5] *$300 million to < $400 million*
[6] *$200 million to < $300 million*

6.60 Compared to the March 2025 submission, the revised financial estimates in the resubmission reflect an approximate [redacted]% reduction in net cost to the PBS/RPBS primarily due to three key factors: (i) the inclusion of an attribute related to seeking medical advice among the MHT-unsuitable patient population (60%), (ii) the separation of discontinuation rate from compliance rate, and (iii) a [redacted]% reduction in the proposed effective price.

6.61 At the March 2025 meeting, the PBAC noted that the financial impact of listing fezolinetant was uncertain and most likely overestimated, as agreed by the DUSC. The uncertainty stemmed from factors including an unclear eligible patient population, inappropriate application of discontinuation rates, potential substitution with MHTs, and unverifiable assumptions regarding MHT suitability and patient uptake (paragraph 7.13, fezolinetant PSD March 2025 PBAC meeting).

6.62 Table 19 outlines the key inputs relied on in the financial estimates.

Table 19: Key inputs for financial estimates

Data	Value		Source and comments
	March 2025	**November 2025**	
Eligible population			
Average prevalence of menopause	Based on females 40-79: 65.4%	Based on females 40-65: 52.21%	The PBAC previously raised concerns about the uncertainty of using average prevalence estimates for menopause and M-S VMS based on weighted age-group averages. It also noted that the assumption that 75% of patients are unsuitable for MHT was unverified, likely overstated and inconsistent with clinical practice (para 6.72, fezolinetant PSD March 2025). The resubmission explained that prevalence data were used due to a lack of incidence data and adjusted the age range to 40–65 years (aligned with DAYLIGHT and SKYLIGHT-1 & -2, using 2026–2031 ABS data). To address PBAC concerns over the 75% MHT-unsuitability population, it assumed only 60% of these patients would seek medical advice (Todorova et al., 2023), resulting in an eligible population of 45.04% (75% × 60%). Revised in Pre-PBAC response to 26.4%.
Average prevalence of M-S VMS	Based on females 40-79: 9.8%	Based on females 40-65: 14.89%	
MHT unsuitable	75%	Unchanged in resubmission.	
Seek medical advice	Not included	60%	
Initiating patient numbers	**Women aged 40-79 ys / Eligible pts *** Y1 [redacted] [redacted] Y2 [redacted] [redacted] Y3 [redacted] [redacted] Y4 [redacted] [redacted] Y5 [redacted] [redacted] Y6 [redacted] [redacted] *Post-menopausal patients (65.4%) with moderate to severe VMS (9.8%), who are unsuitable for MHT (75%).	**Women aged 40-65 ys / Eligible pts **** Y1 [redacted] [redacted] Y2 [redacted] [redacted] Y3 [redacted] [redacted] Y4 [redacted] [redacted] Y5 [redacted] [redacted] Y6 [redacted] [redacted] ** Post-menopausal patients (52.21%) with moderate to severe VMS (14.89%), who are unsuitable for MHT (75%), and seek medical advice (60%).	
Treatment utilisation			
Uptake rate	**Uptake rate / GF / Initiating pts** Y1: [redacted]% [redacted] [redacted] Y2: [redacted]% [redacted] Y3: [redacted]% [redacted] Y4: [redacted]% [redacted] Y5: [redacted]% [redacted] Y6: [redacted]% [redacted] Note: The submission assumed that [redacted] GF patients would transition from private treatment to PBS in mid-2026 and receive the PBS-listed treatment for only six months ([redacted] patients × 0.5 year). This was based on the sponsor's private market forecast.	**Uptake rate / GF / Initiating pts** Y1 [redacted] [redacted]% [redacted] Y2 [redacted]% [redacted] Y3 [redacted]% [redacted] Y4 [redacted]% [redacted] Y5 [redacted]% [redacted] Y6 [redacted]% [redacted] Revised in pre-PBAC to: Y1 [redacted] [redacted]% [redacted] Y2 [redacted]% [redacted] Y3 [redacted]	The PBAC previously considered the uptake rates to be underestimated, particularly if MHT-averse patients are included in the assumptions. Uptake estimates were increased for the first four years and remained the same for the final two years. The resubmission did not provide any justification for the adjustments in uptake rates, particularly given that MHT-averse patients were excluded from the target population. The uptake rates were increased substantially for years 2-6 in the pre-PBAC response.

Data	Value		Source and comments
	March 2025	November 2025	
		[redacted]% Y4 [redacted]7 [redacted]% Y5 [redacted]12 [redacted]% Y6 [redacted]12 [redacted]%	
Discontinuation rate	72.6%, projected as the annual discontinuation rate	The annual rate of 27.4% was estimated from the discontinuation rate reported in DAYLIGHT at 24 weeks (13.72%). Annual discontinuation rate was used to estimate the average treatment duration of 265.29 days (=365.25 days*(1-27.4%)). Average treatment duration for GF patients was assumed to be 6 months (i.e., 183 days).	The PBAC previously noted that using the discontinuation rate as an annual compliance rate was inappropriate, as it failed to account for patients discontinuing treatment being removed from the prevalent pool (para 6.72, fezolinetant PSD March 2025). In response, the resubmission modelled discontinuation (from DAYLIGHT) and compliance (from a real-world study), separately. Given that the resubmission had applied a prevalence approach, patients were not tracked over time in the financial estimates. The trial based one year discontinuation rate was thus uncertain when applied in this context.
Compliance rate		The compliance rate of 77.9% was based on the average of real-world compliance rates across 10 countries for fezolinetant. This was used to estimate the Scripts/Year of 9.48 (365.2 days/pack size of 30 x compliance rate).	The real-world compliance rate (77.9%, based on 10 countries over ~13 months) was higher than the DAYLIGHT study's ≥168-day exposure rate (68.1%, para 5.6, DAYLIGHT CSR), but is consistent with the economic evaluation.
Number of scripts	**Year PBS RPBS Total** **Y1** [redacted]15 [redacted]13 [redacted]15 **Y2** [redacted]16 [redacted]6 [redacted]17 **Y3** [redacted]17 [redacted]6 [redacted]17 **Y4** [redacted]17 [redacted]6 [redacted]17 **Y5** [redacted]17 [redacted]6 [redacted]17 **Y6** [redacted]17 [redacted]6 [redacted]17 Total (**6Years**) [redacted]18	**Year PBS RPBS Total** **Y1** [redacted]19 [redacted]20 [redacted]19 **Y2** [redacted]19 [redacted]20 [redacted]19 **Y3** [redacted]21 [redacted]13 [redacted]21 **Y4** [redacted]15 [redacted]13 [redacted]15 **Y5** [redacted]15 [redacted]13 [redacted]15 **Y6** [redacted]22 [redacted]13 [redacted]22 **Total (6Years)** [redacted]23 Updated in pre-PBAC response (see Table 20)	The resubmission estimated treatment durations as 0.73 years (or 265.29 days, accounting for discontinuations) for initiating patients (excluding GF and accounting for discontinuation) and 0.5 years for GF patients. Total patient-years were then multiplied by 9.48 prescriptions per patient to reflect compliance.

Data	Value		Source and comments
	March 2025	November 2025	
Costs			
Fezolinetant 45 mg	Proposed AEMP=$[redacted], Proposed DPMQ=$[redacted] per 30-day supply	Proposed effective AEMP=$[redacted], Proposed effective DPMQ=$[redacted] per 30-day supply DPMQ updated in pre-PBAC response to [redacted] per 30-day supply	[redacted]% reduction in the proposed effective price, through SPA.
PBS/RPBS split	PBS: 98.95%, RPBS: 1.05%	PBS: 99.05%, RPBS: 0.95%	Values were updated based on PBS data for MHT prescriptions from May 2024 to April 2025. This may be uncertain, as the service volumes should reflect the last full calendar year.
Co-payment	PBS: $7.08, RPBS: $5.33	PBS: $11.89, RPBS: $5.68	
MBS items	GP and specialist visits (items 23 and 36)	Excluded GP and specialist visits, included LFT costs (item 66512, $17.7 per test)	The PBAC previously noted that MBS items 23 and 36 should not be included in savings calculations, as reduced demand would likely be offset by other patients. DUSC highlighted that menopause-related consultations may increase due to the need for follow-up appointments and longer initial consults (para 6.72, fezolinetant, PSD March 2025). The resubmission excluded items 23 and 36 from savings and included item 66512 for LFTs prior to treatment, and then at months 1, 2, 3, 6 and 9, but did not incorporate DUSC's advice regarding additional consultations for patients requiring LFT monitoring. Additionally, as the model used a prevalent approach, each patient received six liver function tests every year instead of receiving 6 tests in their first year, and 1 test per year thereafter. Furthermore, the model has assumed that GF patients will not need any LFT because they are already 6 months into treatment, however they would still require a LFT at month 9.

Source: Table 4.1-1, pp105-106, Table 4.2-1, p107, Table 4.2-2, p108, Table 4.2-3, p108, Table 4.2-4, p109, Table 4.2-5, p109, Table 4.-6, p110, Table 4.2-7 and Table 4.2-8, p111, Table 4.2-10, p114, and Table 4.5-2, p120.

GF=grandfathered, MBS=Medicare Benefits Schedule; MHT=Menopausal hormone therapy, M-S VMS=moderate to severe vasomotor symptoms, LFT=liver function test; PBS=Pharmaceutical Benefits Advisory Committee; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Schedule of Pharmaceutical Benefits; VMS=vasomotor symptoms; Y = year; Ys = years.

Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *6,000,000 to < 7,000,000*
[2] *200,000 to < 300,000*
[3] *300,000 to < 400,000*
[4] *4,000,000 to < 5,000,000*
[5] *100,000 to < 200,000*
[6] *10,000 to < 20,000*
[7] *70,000 to < 80,000*
[8] *20,000 to < 30,000*
[9] *40,000 to < 50,000*
[10] *60,000 to < 70,000*
[11] *80,000 to < 90,000*
[12] *90,000 to < 100,000*
[13] *5,000 to < 10,000*
[14] *50,000 to < 60,000*
[15] *600,000 < 700,000*
[16] *900,000 to < 1,000,000*
[17] *1,000,000 to < 2,000,000*
[18] *7,000,000 to < 8,000,000*
[19] *400,000 to < 500,000*
[20] *500 to < 5,000*
[21] *500,000 to < 600,000*
[22] *700,000 to < 800,000*
[23] *3,000,000 to < 4,000,000*

6.63 Table 20 summarises the estimated changes in patient numbers, script volume and total cost to the government budget as presented in March 2025 submission (blue shaded), resubmission, PSCR and pre-PBAC response.

6.64 The PSCR included a revised the financial model, which it reported included the following amendments:

- Estimated the number of new patients initiating treatment each year by calculating the difference between the treated patient population in the current and previous year. Total patient numbers were unchanged in the PSCR estimates.
- Applied the treatment discontinuation rate to patients initiating fezolinetant each year and tracked persistence over time.
- Revised the treatment compliance to 100% to avoid double counting. (However, this adjustment, was not reflected in the presented revised base case presented in the PSCR). The ESC considered that it was appropriate for compliance and discontinuation to be applied separately in the financial estimates and for these values to be consistent with the economic evaluation.

6.65 The pre-PBAC provided revised estimates, which it reported included the following amendments:

- Revised the eligible population from 45.04% to 26.4%, based on the proportion of post-menopausal women with moderate to severe VMS who are MHT contraindicated or MHT stoppers, excluding the "MHT caution" subgroup 26.4%[12].
- Updated uptake rates based on ESC advice that due to limited treatment options for patients on the PBS, the uptakes rates were underestimated. Uptake was reduced slightly in year 1 and increased substantially in subsequent years, including from [redacted]% to [redacted]% in year 6 (see Table 19).
- Decreased grandfathered patients (5,000 to < 10,000 from 10,000 to < 20,000).
- Updated wholesale mark-ups, AHI fees and dispensing fees as of 1st July 2025.
- Changed the published and effective prices to [redacted] and $[redacted], respectively.

[12] based on a mean estimate from DAYLIGHT, SKYLIGHT, Global Survey (2693-MA-3283), DSP Survey (2693-MA-3284) and CPRD Study [UK Gold] (pre-PBAC response, p2)

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Eligible patients							
March 2025	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-PBAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients electing to receive fezolinetant							
March 2025	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resubmission	[redacted] a10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR	[redacted] a10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-PBAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total fezolinetant scripts (PBS/RPBS)							
March 2025	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-PBAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of fezolinetant to PBS/RPBS							
March 2025	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Resubmission (Change, vs March 2025 submission %)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)
PSCR (Change vs resubmission, %)	$[redacted] ([redacted]%)	$[redacted] ([redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)
Pre-PBAC (Change vs resubmission, %)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)	$[redacted] (-[redacted]%)
MBS costs							
March 2025	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Resubmission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Pre-PBAC	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to government							
March 2025	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Resubmission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Pre-PBAC	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Compiled during the evaluation and Table 4.2-4, p108, Table 4.2-6, p110, Table 4.2-8, p111, Table 4.2-11, p114, Table 4.5-3, p120, Table 4.5-4, p121, PSCR, and Pre-PBAC.

MBS=Medicare Benefits Schedule; MHT=Menopausal hormone therapy, M-S VMS=moderate to severe vasomotor symptoms; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Schedule of Pharmaceutical Benefits, VMS=vasomotor symptoms.

[a] 'unsuitable for MHT' defined as: March 2025 = ; Resubmission = ; PSCR = ; Pre-PBAC = MHT contraindicated, MHT stoppers due to side-effects or inefficacy after 3 months.

[a] The total includes 40,000 to < 50,000 prevalent patients (excluding GF patients) and 10,000 to < 20,000 GF patients.

Blue shading indicates data previously seen by the PBAC.
The redacted values correspond to the following ranges:
[1] *200,000 to < 300,000*
[2] *300,000 to < 400,000*
[3] *1,000,000 to < 2,000,000*
[4] *100,000 to < 200,000*
[5] *900,000 to < 1,000,000*
[6] *90,000 to < 100,000*
[7] *500,000 to < 600,000*
[8] *70,000 to < 80,000*
[9] *800,000 to < 900,000*
[10] *60,000 to < 70,000*
[11] *80,000 to < 90,000*[12] *100,000 to < 200,000*
[13] *20,000 to < 30,000*
[14] *40,000 to < 50,000*
[15] *50,000 to < 60,000*
[16] *300,000 to < 400,000*
[17] *600,000 to < 700,000*
[18] *700,000 to < 800,000*
[19] *7,000,000 to < 8,000,000*
[20] *400,000 to < 500,000*
[21] *3,000,000 to < 4,000,000*
[22] *2,000,000 to < 3,000,000*
[23] *$70 million to < $80 million*
[24] *$100 million to < $200 million*
[25] *$200 million to < $300 million*
[26] *$800 million to < $900 million*
[27] *$20 million to < $30 million*
[28] *$30 million to < $40 million*
[29] *$40 million to < $50 million*
[30] *$200 million to < $300 million*
[31] *$10 million to < $20 million*
[32] *$0 to < $10 million*
[33] *$50 million to < $60 million*
[34] *$60 million to < $70 million*

6.66 The total net cost to PBS/RPBS over the first six years of use decreased from $800 million to < $900 million in the March 2025 submission to $200 million to < $300 million in the resubmission. The total net cost to PBS/RPBS over the first 6 years of listing was reduced to $100 million to < $200 million in the pre-PBAC revised estimates, although the total costs for years 5 and 6 of the estimates were higher than in the PSCR estimates. Revisions in the pre-PBAC response substantially reduced the net costs to the MBS from $30 million to < $40 million to $20 million to < $30 million over the first six years of use.

6.67 The financial impact remained uncertain for the following reasons:

- In the Pre-PBAC response , the sponsor agreed to refine the eligible population to those who are contraindicated to MHT, or who have discontinued due to side effects or lack of efficacy after 3 months. A global cross-sectional survey of postmenopausal women 40-65 years experiencing M-S VMS in the last 12 months found that only 8%-12% were contraindicated for MHT (i.e., who have been assessed by a physician and for whom MHT was deemed inappropriate due to certain conditions). Women categorised as MHT-stoppers were reported to range

from 5%–11%[13]. The ESC considered that the population truly unsuitable for MHT (i.e., contraindicated and/or experiencing severe AEs) applied in the estimates should be no more than 10-15%, consistent with the populations identified in Nappi (2021) as MHT unsuitable and MHT stoppers; and Todorova (2023) above, as MHT contraindicated and MHT stoppers. The pre-PBAC response reduced the proportion of eligible menopausal patients from 45% to 26.4%. The pre-PBAC response stated that this was based on a mean estimate from DAYLIGHT, SKYLIGHT, Global Survey (2693-MA-3283), DSP Survey (2693-MA-3284) and CPRD Study [UK Gold], however these calculations could not be verified.

- The evaluation and the ESC considered the uptake rates for fezolinetant in those medically unsuitable for MHT may be underestimated. Although the resubmission excluded MHT-averse patients and increased uptake by [redacted]%–[redacted]% during the first four years, the ESC considered that limited options in this population suggest potentially higher uptake. This was revised in the pre-PBAC response, with uptake rates increased substantially from years 2 onwards, up to [redacted]% in year 6.

6.68 Overall, the evaluation and the ESC considered that the net costs associated with the PBS listing of fezolinetant were highly uncertain and likely overestimated.

Quality Use of Medicines

6.69 The resubmission outlined activities to support the quality use of medicines, including (i) providing patients with accessible safety information via QR codes linked to up-to-date Consumer Medicines Information; (ii) offering prescribers clear liver function monitoring guidance in the revised Product Information and developing practical monitoring tools pending regulatory approval; and (iii) ongoing global safety data collection (no Australia-specific post-marketing studies planned), while maintaining engagement with regulators to ensure effective risk management and support for fezolinetant safe use in Australia.

Financial Management – Risk Sharing Arrangements

6.70 The sponsor proposed a risk-sharing arrangement (RSA), based on a tiered subsidisation cap for fezolinetant. The proposed RSA is outlined in Table 21.

[13] Nappi RE. et al., Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause. 2021 May 24;28(8):875-882. doi: 10.1097/GME.0000000000001793.

Table 21: Proposed RSA for fezolinetant (rebate payable on amount above cap)

RSA criteria	Deed Year 1	Deed Year 2	Deed Year 3	Deed Year 4	Deed Year 5
Commonwealth PBS/RPBS expenditure between >[redacted]% - ≤[redacted]% of agreed cap	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Commonwealth PBS/RPBS expenditure between >[redacted]% - ≤[redacted]% of agreed cap	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Commonwealth PBS/RPBS expenditure >[redacted]% of agreed cap	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Source: Table 4.6-3, p124 of the resubmission.
PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme; RSA=Risk Share Agreement

6.71 The resubmission proposed a rebate of [redacted]% for expenditure between [redacted]% and [redacted]% of expected utilisation.

6.72 The ESC considered that the proposed three-tiered RSA was overly complex, and that a single tier RSA with a hard cap may be more appropriate. The ESC noted that RSA caps would also need to be reduced to reflect updates to financial estimates.

6.73 The pre-PBAC response proposed a revised, single-tier RSA, which requested that that the caps be set at [redacted]% above the revised financial estimates to account for the uncertainty in epidemiology of "MHT contraindicated' and "MHT stoppers", and proposed a rebate of [redacted]% on Commonwealth expenditure exceeding the agreed subsidisation cap in any one year (Table 22).

Table 22: Proposed RSA for fezolinetant in post-menopausal women with moderate to severe VMS who are unsuitable for MHT

RSA Criteria	Deed Year 1	Deed Year 2	Deed Year 3	Deed Year 4	Deed Year 5
Commonwealth Expenditure ([redacted]% financial estimates)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: table 2, pre-PBAC response.
RSA, risk sharing agreement, SC, subsidisation cap.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of fezolinetant, for the treatment of moderate to severe menopause-related vasomotor symptoms (VMS). The PBAC considered that there is a clinical need for non-hormonal treatments in patients who cannot take menopausal hormone therapy (MHT) (i.e., are contraindicated, have experienced side-effects necessitating withdrawal, or have had an inadequate response). The PBAC considered that the revised proposed clinical place for fezolinetant presented in the pre-PBAC response reflected a more well-defined population which addressed the Committee's previous concerns regarding the clinical place and comparator for fezolinetant. The PBAC was satisfied that fezolinetant provides, for some patients, a significant improvement in efficacy over no treatment. The PBAC considered that uncertainty remained regarding the cost-effectiveness of fezolinetant, and noted the potential for use outside the intended narrow patient population and concerns about liver toxicity. The PBAC advised these issues could be managed via a reduction in the

price for fezolinetant, in combination with a risk sharing arrangement (RSA) and regular monitoring of liver function.

7.2 The PBAC considered that for patients with a contraindication to MHT as defined by the pre-PBAC revised restriction, there are few treatment options that are accessible and PBS listed. The PBAC noted that comments from clinicians and individuals experiencing menopause-related VMS supported the need for alternative treatment options for those truly unable to take MHT. The PBAC acknowledged comments from organisations that there is a particular need for subsidised non-hormonal treatments for those in whom menopause has sudden onset (for example, hormone-based cancer treatment).

7.3 The PBAC recalled that it previously considered that the clinical place proposed for fezolinetant would need to be more appropriately and tightly defined (paragraph 7.2, fezolinetant PSD, March 2025 PBAC Meeting). The PBAC agreed with the ESC that the inclusion of patients with "MHT caution" would still capture a large number of patients who could be appropriately treated with oral or transdermal MHT. The PBAC considered the revised population proposed in the pre-PBAC response, which included only those contraindicated to MHT, or who discontinued MHT due to adverse effects or lack of efficacy (paragraph 3.4) to be more appropriate.

7.4 The PBAC recalled that it previously considered that the requested restriction would not limit first-line access to patients with medical reasons to avoid MHT (paragraph 7.4, fezolinetant PSD, March 2025 PBAC Meeting). The PBAC considered that the updated restriction provided in the resubmission addressed some of its previous concerns (paragraphs 3.3-3.4), and the majority of outstanding issues regarding the restrictions were addressed in changes proposed in the PSCR and pre-PBAC response (paragraph 3.4), including:

- Changing authority level to Authority Required (Telephone/Online).
- Revised population, excluding MHT caution.
- Inclusion of a definition of MHT contraindication.
- Prescribing instruction regarding consideration of transdermal MHT prior to considering treatment with fezolinetant.
- Caution regarding LFT monitoring requirements.
- Continuing treatment by nurse practitioners.

The PBAC considered minor additional revisions to the definition of MHT contraindicated would be appropriate, i.e.:

- clarification regarding age <60yrs requirement pertains to initiation of treatment.
- Addition of 'current or history of' breast cancer.
- Removal of category for significant liver disease, which is also a contraindication to fezolinetant.

7.5 The PBAC noted the sponsor's proposed caution specifying that fezolinetant is intended for use in post-menopausal patients, but considered that this addition was unnecessary. The PBAC considered that it would be reasonable for the restrictions to

remain silent regarding treatment in peri-menopausal patients, noting that the indication is menopause-related VMS, consistent with the TGA indication in the PI.

7.6 The PBAC noted that input from clinicians provided as a written statement indicated they were supportive of inclusion of a definition of moderate-severe VMS in the restrictions. The PBAC considered that it would be reasonable to include a definition of moderate to severe VMS in line with the trial inclusion criteria (see paragraph 3.4), and for the restrictions to specify the minimum of 7 moderate-to-severe hot flushes (VMS episodes) per day (average) as per the clinical trials, and as suggested in the clinician statement.

7.7 The PBAC noted that the revised restrictions were intended to exclude patients who could be treated with MHT, in which case MHT would not be a relevant comparator. The PBAC recalled that it previously considered that the nomination of 'no treatment' as the main comparator was not appropriate for requested PBS patients who are contraindicated to MHT, or who have discontinued MHT due to adverse effects (AEs) (paragraph 7.6, fezolinetant PSD, March 2025 PBAC meeting). The PBAC noted that the comparator was unchanged in the resubmission supported by a consensus statement that existing non-hormonal treatments are infrequently prescribed and are not routine care. However, the PBAC also noted that real-world prescribing data commissioned by the sponsor using primary care electronic records in women aged 45-65 years with diagnosis/symptoms related to VMS suggested that 21-28% of patients received non-hormonal treatments. The PBAC noted that there are very limited data to inform any analysis of comparative efficacy and safety between fezolinetant and other non-hormonal treatments for VMS. However, overall the PBAC considered that 'no treatment' was the appropriate main comparator for patients truly unsuitable for MHT.

7.8 The PBAC recalled that it previously considered that the claim of superior effectiveness over no treatment was likely supported by the evidence, however the clinical significance was uncertain (paragraphs 7.8, fezolinetant PSD, March 2025 PBAC Meeting). The PBAC noted that no new evidence was presented with the resubmission, but that additional *post hoc* subgroup analyses for the DAYLIGHT and SKYLIGHT trials excluding "MHT averse" patients (those who had made an informed choice not to use hormone therapy after discussion with a clinician) were provided. The PBAC considered this subgroup to be more reflective of requested population and noted that the observed efficacy was similar to that for the overall trial populations. The PBAC noted that the resubmission's economic model continued to use the trial ITT populations, which it considered was reasonable given the comparable results in the *post hoc* analyses. Although the point estimates for the reduction in VMS frequency in DAYLIGHT at Week 12/24 (1.87 to 1.96) did not exceed the nominated minimally clinically important difference (MCID; ≥2 hot flushes/day), the reduction did exceed this MCID in the SKYLIGHT trials (2.51 to 2.75, pooled results). The PBAC noted the submission and pre-PBAC response presented pooled results for the DAYLIGHT and SKYLIGHT trials in MHT unsuitable patients, and a 50% reduction in VMS frequency was observed in 64% of patients treated with fezolinetant versus 41% of patients treated with placebo, a 75% reduction in 44% versus 23% and a 100% reduction in

17% versus 7%. Further, the PBAC considered the reduction in mean severity of VMS symptoms was clinically significant with point estimates of 0.30-0.44 in DAYLIGHT and 0.24-0.31 in SKYLIGHT versus a likely MCID of 0.225. Overall, the PBAC considered that the claim of superior effectiveness over no treatment was supported by the evidence.

7.9 The PBAC recalled that it previously considered the safety of fezolinetant to be inferior compared to placebo, particularly given the risks of hepatotoxicity associated with fezolinetant and lack of long-term data (paragraphs 6.38 and 7.9, fezolinetant PSD, March 2025 PBAC Meeting). The PBAC noted that the fezolinetant product information (PI) has been revised to include clear requirements for liver function monitoring however, the PBAC maintained its view that the safety of fezolinetant is inferior to placebo.

7.10 Compared to the March 2025 submission, the cost-utility analysis in the resubmission was largely unchanged. Key changes to the resubmission's model included a price reduction for fezolinetant (DPMQ $[redacted] to $[redacted]), change in the compliance rate for fezolinetant (from 100% to 77%), and inclusion of LFT monitoring costs (see Table 8), resulting in an ICER of $25,000 to < $35,000 per QALY. The PBAC considered that its previous concern regarding the exclusion of costs associated with LFT monitoring and significant AEs were partially addressed in the resubmission, but noted LFT costs from the second year onwards were inappropriately not included (Table 8). The PBAC considered an annual test from year 2 onwards, consistent with the PI recommendation for ongoing monitoring, should be included. The PBAC agreed with the ESC and pre-PBAC response that the use of a 77.9% compliance rate derived from real world data was reasonable (paragraphs 6.46). However, the PBAC agreed with the ESC that additional changes to the model would provide a more reliable estimate of cost-effectiveness, specifically that:

- a 5 year time horizon would be more appropriate given the short (52 week) duration of the trial and likely background decline in symptoms,
- the fezolinetant discontinuation rate beyond week 24 should be the same as for weeks 0-24 (2.4% from DAYLIGHT) to maintain consistency with the assumed discontinuation rate for the no treatment arm (paragraphs 6.43 - 6.45).

The PBAC noted that these changes resulted in an increase in the ICER from $25,000 to < $35,000 to $25,000 to < $35,000 per QALY gained (paragraph 6.56). The PBAC recalled that it previously considered that an ICER in the range of $15,000 to < $25,000 to $25,000 to < $35,000 per QALY would be acceptable (paragraph 7.11, fezolinetant PSD, March 2025 PBAC Meeting), and noted that a price reduction would be required to achieve an acceptable ICER with the revised inputs. The PBAC noted that the price required for an ICER of $15,000 to < $25,000 per QALY gained was consistent with the cost of MHT, which provided additional confidence that fezolinetant would remain acceptably cost-effective where there was use outside the intended population.

7.11 The PBAC recalled that it previously considered the financial estimates provided in the March 2025 submission ($800 million to < $900 million over 6 years) to be uncertain,

unacceptably high, and likely substantially overestimated for the requested population (paragraph 7.13, fezolinetant PSD, March 2025 PBAC Meeting). The resubmission's updated financial estimates were based on the same epidemiological approach, but included adjusted inputs (as per paragraph 6.58 and Table 19), which resulted in an approximate 70% reduction in net cost to the PBS/RPBS primarily due to: the inclusion of an assumption that only 60% of MHT-unsuitable patients would seek treatment; separation of discontinuation rate from compliance rate; and reduction in the proposed effective price.

7.12 The PBAC agreed with the ESC that the estimated 75% of post-menopausal women with moderate to severe VMS (45% excluding those not seeking treatment) remained implausibly high. The PBAC considered that this was partially addressed in the pre-PBAC response alongside tightening of the restriction to exclude the MHT caution group (paragraphs 7.3 and 7.4), but considered that the updated estimate of 26.4% remained overestimated and likely included some patients who would be suitable for MHT. The PBAC considered that an estimate of 10-15% would be more reasonable for the revised intended population who cannot be treated with MHT, especially in the context of the high uptake rates applied in the pre-PBAC revisions.

7.13 The PBAC noted that the additional cost to the MBS for LFTs was not insubstantial and considered that the financial estimates should include 6 LFTs per patient in the first year of treatment and one LFT per patient for the following years, consistent with the updated PI guidance regarding liver function monitoring.

7.14 The PBAC recalled that it previously considered that an RSA is likely to be essential to manage risks of usage outside the revised PBS restriction, usage (duration on treatment) beyond expectations, and uncertainty around the percentage of Australians eligible for treatment. The PBAC noted the pre-PBAC response proposed an RSA with financial caps based on [redacted]% of estimated use and a rebate of [redacted]% for use exceeding the caps. The PBAC considered that this did not adequately mitigate for the uncertainty in the estimate of the population and duration of treatment as well as concern of use outside restriction. The PBAC considered the financial caps for an RSA could be based on the estimated use in the pre-PBAC response (with up to 26.4% not treated with MHT) provided the fezolinetant price was consistent with a $15,000 to < $25,000 per QALY gained ICER (see paragraph 7.10). The PBAC advised a price for fezolinetant consistent with an ICER of $25,000 to < $35,000 per QALY gained would only be appropriate if combined with a reduction in the proportion not treated with MHT that was more in line with the 10-15% estimate as per paragraph 7.12. However given the uncertainty in the estimate, the PBAC considered that the most reliably cost-effective position was using a price consistent with an ICER of $15,000 to < $25,000 per QALY. The PBAC considered that the rebate for use exceeding the caps should be close to [redacted]%. The PBAC considered that an RSA with these conditions would address remaining uncertainty regarding the total number of patients likely to be treated with fezolinetant and the potential for use outside the intended population.

7.15 The PBAC recommended that fezolinetant should not be treated as interchangeable on an individual patient basis with any other drugs.

7.16 The PBAC advised that fezolinetant is suitable for prescribing by medical practitioners only as initial treatment, and by medical practitioners and nurse practitioners as continuing treatment.

7.17 The PBAC advised that the early supply rule should be applied to fezolinetant.

7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for fezolinetant:

- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, although reductions in the frequency and severity of VMS are expected, the magnitude of benefit is somewhat uncertain;
- The treatment is not expected to address a high and urgent unmet clinical need as there are other non-PBS and off-label treatments available;
- It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.19 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FEZOLINETANT						
fezolinetant 45 mg tablet, 30		NEW	1	30	5	VEOZA
Concept ID	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners					
	Benefit type: ☒ Authority Required (Telephone/ Online PBS Authorities system)					
	Prescribing rule level:					
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
	Caution: Baseline hepatic laboratory tests should be performed for all patients before initiating fezolinetant. Follow-up hepatic laboratory tests should be performed monthly for the first 3 months, at 6 months and at 9 months of therapy, and thereafter periodically based on clinical judgement.					
	Restriction Summary [new1] / Treatment of Concept: [new1A]					
	Indication: Moderate to severe menopause-related vasomotor symptoms (VMS)					
	Clinical criteria:					
	Patient must be experiencing an average of at least 7 moderate-to-severe VMS episodes per day					
	AND					
	Clinical criteria:					
	Patient must be unsuitable to receive menopausal hormone therapy (MHT) due to experiencing at least one of the following: (i) has a condition for which MHT is contraindicated (ii) has discontinued MHT due to side effects/ intolerance (iii) has discontinued MHT after at least 3 months of therapy due to lack of efficacy.					
	Treatment criteria					
	Must be treated by a health practitioner who is any of: (i) a medical practitioner, (ii) a nurse practitioner who is continuing treatment with this medicine that was initiated by a medical practitioner as a PBS benefit.					
I	**Prescribing Instructions:** Prior to receiving treatment with this drug for this condition, transdermal MHT should be considered for patients who developed side effects or intolerance to oral MHT.					
	Prescribing Instructions: Moderate VMS is defined as a sensation of heat with sweating, but able to continue activity. Severe VMS is defined as a sensation of heat with sweating, causing cessation of activity.					

	Prescribing Instructions: A contraindication to menopausal hormone therapy (MHT) is defined as at least one of the following: (i) age 60 years or older prior to initiation of any treatment for VMS, (ii) previous venous thromboembolism, (iii) previous transient ischaemic attack, stroke or acute myocardial infarction, (iv) uncontrolled hypertension, (v) current or past history of estrogen-dependent cancer (e.g. endometrial or breast cancer), (vi) undiagnosed vaginal bleeding (may include estrogen-dependent cancer), • high risk of breast cancer after individual risk assessment, State the relevant contraindication(s) with the first authority application where applicable.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Astellas is working proactively with the Department of Health to improve womens health via access to Fezolinetant on the PBS for all suitable Australian women, as soon as possible