Fezolinetant: A Promising New Non-hormonal Drug Against Menopausal Symptoms

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CRITICAL REVIEW

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ABSTRACT

During menopause, up to 80% of individuals experience vasomotor symptoms, such as hot flashes, that severely impact quality of life.[1] Fezolinetant is a novel oral drug that shows promise in treating hot flashes by acting as a neurokinin 3 receptor antagonist that restores hypothalamic thermoregulation.[2] This review explores the effectiveness of Fezolinetant in reducing menopausal symptoms compared to the current pharmacological standard of care. We evaluate the strengths of Fezolinetant as an alternative treatment for patients that are eligible for traditional hormone replacement therapy and outline current limitations of the medication. The potential benefits of Fezolinetant warrant further research and post-market clinical trials to continue monitoring its efficacy and safety.

INTRODUCTION

Vasomotor symptoms, commonly known as hot flashes, include sensations of heat, sweating, anxiety, and chills lasting one to five minutes. These symptoms occur during menopause when reduced estrogen levels disrupt hypothalamic regulation of core body temperature.[3,4] As a selective neurokinin 3 receptor antagonist, Fezolinetant blocks neuropeptide neurokinin B (NKB) from binding to kisspeptin–neurokinin B–dynorphin (KNDy) neurons, which helps restore the sensitivity of the hypothalamic thermoregulatory centre to normal levels.[2] NKB stimulates KNDy neurons in the thermoregulatory centre and acts on estrogen inhibited neurokinin 3 receptors.[5] This review discusses the efficacy, safety, strengths and limitations of Fezolinetant as a novel treatment for vasomotor symptoms of menopause.

REVIEW FINDINGS

DRUG EFFICACY

In the phase III study SKYLIGHT 1, a randomised, double-blind trial was conducted between placebo, 30mg, and 45mg Fezolinetant groups. The results from this trial indicate that Fezolinetant significantly reduces in the frequency and severity of vasomotor symptoms compared to placebo over the course of 52 weeks.[6] The high-quality methods in this study ensured that confounding factors were reduced and the notably high potential for placebo bias was limited. Similar results were observed in SKYLIGHT 2, further validating the efficacy of this treatment.[5] Additionally, the study was designed to be highly generalisable by recruiting a diverse population of study participants. The inclusion criteria consisted of female-born individuals aged 40 years to 65 years, BMI from 18 to 38 kg/m^2, an absence of clinically significant findings on mammogram and pap test, and willingness to undergo a transvaginal ultrasound and endometrial biopsy.[5] The SKYLIGHT study took place across 97 facilities, including the United States, Canada, Czech Republic, Hungary, Poland, Spain, and the United Kingdom.[5]

Another study, Moonlight 1, involved 302 participants sampled from a variety of Asian countries.[7] For data collection, researchers tracked vasomotor symptoms using various self-reported methods that measured a range of relevant effects. In SKYLIGHT 2, they used an electronic hot flashes diary with a reference guide that outlined mild to moderate and severe symptoms. Menopause Specific Quality of Life (MENQOL) is a 29-item reporting tool that was used to measure vasomotor, psychosocial, physical, and sexual symptoms. The study also used Patient Reported Outcomes Measurement Information System Sleep Disturbance (PROMIS SD) to track sleep disturbances. The extensive scope of symptoms measured in this experiment, ranging from direct indicators of hot flashes to indirect symptoms such as sleep quality, strengthened the quality of the study. After 12 weeks in SKYLIGHT 2, there was a reduction in mean daily vasomotor symptom frequency from baseline by 58.64% in the 30mg group and 64.27% in the 45mg group, compared to 45.35% in the placebo group. After 12 weeks of treatment in the three randomized groups (30mg, 45mg, placebo), participants on placebo were randomly selected to begin the 30mg or 45mg treatment. Despite a placebo effect, there was a statistically significant difference between the treatment and placebo groups throughout the entire 52 week period. Regarding patient-reported sleep disturbances, only the 45 mg group reported a statistically significant difference at 12 weeks.[5]

Limitations of this literature exist due to a reliance on self-reported methods to gather data. Patient-reported symptoms of sleep disturbance have inherent biases as symptoms are subject to variability given that each participant has different basal levels and interpretations of sleep quality. Furthermore, self-reported methods are susceptible to response bias, the tendency for participants to respond inaccurately, which can contribute to the placebo effect. Another discrepancy in SKYLIGHT 1 was that data was only collected from participants that used the interactive diary and had greater than 85% compliance in treatment.[6] This may introduce some degree of bias, where results reflect a specific subset of participants that are more likely to report symptoms, which reduces the study's applicability to clinical settings. Overall, the use of self-reported methods to gather data may not have accurately reflected the efficacy of Fezolinetant.

SAFETY

SKYLIGHT 4, a 52-week Phase III trial, investigated the safety of 30mg and 45mg Fezolinetant dosages using a sample of 1830 participants aged 40-55. Participants who took at least one dose of the study drug were included in the safety analysis. The results showed that treatment emergent adverse events occurred in 63.9% of the 45mg group, 67.9% in the 30mg group, and 64.1% of the placebo group.[8] Notably, 4.3% of participants in the control group withdrew due to the treatment-emergent adverse effects, compared to 5.6% for the 30-mg group and 4.6% for the 45-mg group.[8]

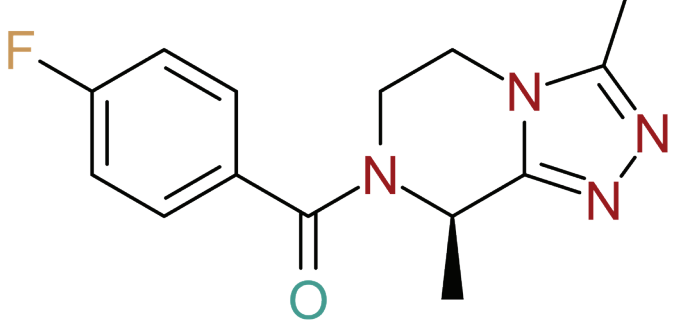
Treatment-related risks of endometrial cancer and endometrial hyperplasia (a precancerous condition where there is an irregular thickening of the uterus) continue to be a concern in examining the safety of Fezolinetant. One case of endometrial malignancy was reported in the 30mg group, while no occurrences of malignancy were reported in the 45mg or placebo group.[8] Changes in secondary endpoints, endometrial thickness, bone mineral density, and

trabecular bone scores, were consistent across all three groups. These results, alongside the low withdrawal rates of SKYLIGHT 4, support the safety of Fezolinetant use over a period of 52 weeks.

The authors of the SKYLIGHT studies were affiliated with and received funding from Astellas Pharma Inc, the proprietor of Fezolinetant, which poses potential for bias. Further peer review and phase IV post-market studies from unbiased sources are necessary to confirm the results of these trials. Since Fezolinetant was recently FDA-approved in May 2023 (Astellas Pharma has yet to submit an application for drug approval to Health Canada), there exists gaps in literature regarding the long-term use of the drug, especially considering that menopausal vasomotor symptoms can persist for about 11.8 years.[7] It is suggested that longitudinal research and post-market evaluation studies be done on an ongoing basis as the drug continues to be used in the consumer market.

APPLICATIONS AND PRACTICALITY

From the data obtained from Phase I, II and III clinical trials, Fezolinetant shows promise for populations of symptomatic individuals undergoing the early stages of menopause. Currently, estrogen and progesterone hormone replacement therapy are the most common treatments for menopause. As a non-hormonal treatment, the drug is accessible for patients who are ineligible or contraindicated for current treatment methods. These agents mimic the neuromodulation effects of estrogen produced by the ovaries on the hypothalamus prior to menopause. However, hormone replacement therapy treatment is only recommended for individuals younger than 60 years old and within 10 years of menopause onset due to risks of coronary heart disease, stroke, dementia, bone loss, and venous thromboembolism.[10] Furthermore, individuals with a history of breast cancer are not candidates for estrogen hormone treatment as the additional estrogen can contribute to tumour growth.[11] With up to 80% of individuals experiencing the vasomotor symptoms of menopause, the drug has potential to restore quality of life in individuals who experience anxiety, poor quality of sleep and occupational disturbances related to these symptoms.[1] Unfortunately, the estimated marketed price of Fezolinetant ($500 for a 1-month supply) raises affordability concerns compared to current treatment options.[12] In comparison, other non-hormonal options such as SSRIs range from $4 to $200 USD in monthly costs.[13] Consequently, the affordability factor can potentially result in low usage rates for Fezolinetant.



CONCLUSION

The development of Fezolinetant, a neurokinin 3 receptor antagonist, offers a promising new treatment option for individuals who are ineligible for traditional hormone therapies. Although current evidence from the SKYLIGHT studies suggests that Fezolinetant has potential to be an effective and safe treatment option, further Phase IV research is required to continue to investigate the long-term efficacy and safety of the drug. Overall, options for the treatment of vasomotor symptoms for individuals who are transitioning into menopause have historically been quite limited, and the development of new therapeutic modalities like Fezolinetant has significant potential to improve the quality of life and health outcomes of impacted individuals.

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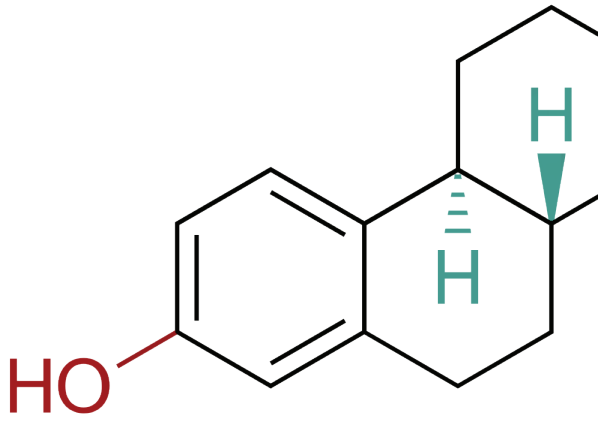

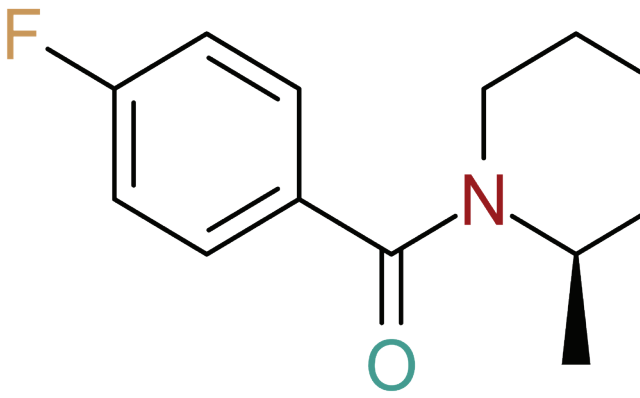

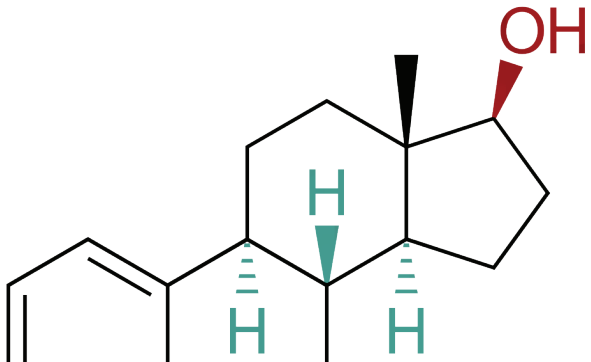

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