CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216578Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216578
PDUFA Goal Date	May 22, 2023
OSE TTT #	2022-290
Reviewer Name	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	May 5, 2023
Subject	Evaluation of Need for a REMS
Established Name	Fezolinetant
Trade Name	Veozah
Name of Applicant	Astellas Pharma Global Development, Inc.
Therapeutic Class	Neurokinin 3 (NK3) receptor antagonist
Formulation(s)	45 mg oral tablet
Dosing Regimen	45 mg orally once daily with or without food

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Veozah (fezolinetant) is necessary to ensure the benefits outweigh its risks. Astellas Pharma Global Development, Inc. submitted a New Drug Application (NDA) 216578 for fezolinetant with the proposed indication for the treatment of moderate to severe vasomotor symptoms due to menopause.[1] The serious risk associated with fezolinetant is increased hepatic transaminases. The applicant did not propose a REMS or risk management plan with this application.

Fezolinetant appeared efficacious in the co-primary endpoints of the mean change in the frequency and severity of moderate to severe vasomotor symptoms at Weeks 4 and 12. The Division of Urology, Obstetrics, and Gynecology (DUOG) recommends approval for moderate to severe vasomotor symptoms due to menopause. DRM has determined that a REMS is not needed to ensure the benefits of fezolinetant outweigh its risks. Transaminase levels returned to pretreatment or near pretreatment levels without sequelae while continuing fezolinetant, upon dose interruption, or with discontinuation. The risk of hepatic transaminase elevations will be communicated in labeling in warnings and precautions and contraindicating the use of fezolinetant in patients with known cirrhosis. The risk of hepatic transaminase elevation is managed for other products in this manner, and at the time of this review, (b) (4) The Prescribing Information for fezolinetant also includes instructions to prescribers to monitor hepatic transaminase levels at baseline and at months 3, 6, and 9 of fezolinetant therapy, and at any point that patients exhibit symptoms of liver injury. At this time, additional risk mitigation measures beyond labeling are not necessary to ensure the benefits outweigh the risks of fezolinetant.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Veozah (fezolinetant)[a] is necessary to ensure the benefits outweigh its risks. Astellas Pharma Global Development, Inc. (Astellas) submitted a New Drug Application (NDA) 216578 for fezolinetant with the proposed indication of treatment of moderate to severe vasomotor symptoms due to menopause.[1] This application is under review in the Division of Urology, Obstetrics, and Gynecology (DUOG). The applicant did not submit a proposed REMS or risk management plan with this application.

[a] Section 505-1(a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2. Background

2.1. Product Information

Fezolinetant, a new molecular entity, is a small molecule, nonhormonal, selective neurokinin 3 (NK3) receptor antagonist, which blocks neurokinin B (NKB) from binding to the kisspeptin, neurokinin B, dynorphin (KNDy) neuron. The KNDy neuron modulates activity in the hypothalamus' thermoregulatory center, which in turn modulates the moderate to severe vasomotor symptoms associated with menopause. Prior to menopause, the KNDy neurons are inhibited by estrogen and stimulated by NKB. As estrogen decreases during menopause, NKB has less opposition, and increases KNDy neuronal activity. This results in KNDy neuron hypertrophy, altered thermoregulatory activity, and vasomotor symptoms ("hot flashes" or "hot flushes").[2]

Fezolinetant is proposed as a 45mg oral tablet taken once daily with or without food. The effective half-life of fezolinetant is proposed as 9.6 hours[3] and while primarily excreted in urine, fezolinetant is extensively metabolized by CYP1A2.[2] Due to this, the use of fezolinetant with inhibitors of CYP1A2 is contraindicated in proposed labeling, as CYP1A2 inhibitors increase the AUC of fezolinetant from 2 to 9.4 times, dependent on strength.[1] Fezolinetant is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216578 relevant to this review:

- 03/22/2022: Astellas informed the Agency of the intent to use a Rare Pediatric Disease Priority Review Voucher (PRV) for the review of fezolinetant[4]
- 06/22/2022: NDA 216578 submission for the treatment of moderate to severe vasomotor symptoms due to menopause received
- 12/02/2022: The Agency sent a Late-Cycle Meeting Background package to the applicant that indicated that a REMS for fezolinetant was not planned[5]
- 01/23/2023: The Agency sent a clinical Information Request to Astellas requesting additional information on cancer screening for trial subjects and information on specific subjects who developed cancer during the studies[6]
- 01/27/2023: Astellas responded to the Agency's January 23, 2023, Information Request with the requested information[7]
- 02/17/2023: The Agency notified the applicant that the January 27, 2023 submission constitutes a major amendment, and the user fee goal would be extended to May 22, 2023[8]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Vasomotor symptoms (VMS) are sudden sensations of heat usually in the upper body, such as the head, neck, and chest/upper back. These symptoms usually last from 1-5 minutes and can include perspiration, flushing, chills, clamminess, and occasionally, anxiety and heart palpitations.[9] Patients who experience VMS average 17 hot flashes and 11 night sweats weekly.[10] VMS may disrupt multiple areas of a patient's life, including sleep, concentration, mood energy, and sexual activity.[b] Up to 80% of women experience these symptoms during menopause, and symptoms have an average duration of 7.4 years.[11][c]

3.2. Description of Current Treatment Options

The American College of Obstetricians and Gynecologists' 2014 Practice Bulletin for the Management of Menopause includes recommendations for systemic hormone therapy (HT) and alternative options for treatment of VMS.[12] HT comprised of estrogen alone or in combination with progestin, administered orally or transdermally, was recommended as the most effective therapy. A meta-analysis of 24 randomized, controlled trials found that HT provided a 75% reduction in hot flush frequency in women who took oral estrogen or estrogen/progestin versus placebo. Low-dose HT is effective without excess adverse events, and the Heart Outcomes Trial evaluated efficacy of different estrogen doses on VMS found that all lower dose HT (0.3 – 0.45 mg/day oral conjugated equine estrogen, 0.5 mg/day oral micronized estradiol, 5 mcg/day of ethinyl estradiol, and 0.025 – 0.0375 mg/week of transdermal estradiol was as effective as conjugate equine estrogens dose of 0.625 mg/day). The risks of HT include thromboembolic disease and breast cancer. The Women's Health Initiative (WHI) study found an increased risk of breast cancer, coronary heart disease, stroke, and venous thromboembolism after 5 years taking a combined HT. In women taking estrogen-only, there was an increase in thrombotic events. Products for HT containing progesterone and estrogen have Boxed Warnings for cardiovascular disorders and increased risk of dementia.

Selective serotonin reuptake inhibitor (SSRI) and selective serotonin-norepinephrine reuptake inhibitors (SSNRI) are nonhormonal alternatives for VMS treatment. Although appearing less effective than HT, paroxetine 7.5 mg/day is the only SSRI that is FDA approved for VMS treatment. No SSNRI's are FDA approved for VMS treatment. Adverse events with SSRI's include nausea, dizziness, dry mouth, nervousness, constipation, sexual dysfunction, sweating, and constipation.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

While not FDA-approved for VMS, clonidine and gabapentin are used off-label to treat VMS. Safety and efficacy data in the population with VMS is limited, but they appear less efficacious than HT. Side effects seen with clonidine include dry mouth, drowsiness, and insomnia, and side effects for gabapentin include dizziness, somnolence, and peripheral edema.

The herbal remedies of phytoestrogen supplements, dong quai, and black cohosh are used as over-the-counter alternatives to prescription medication by some patients. These products are not regulated by the FDA and may interact with other medications the patient is taking, including dong quai and warfarin, and liver toxicity has been reported with the use of black cohosh supplements. As HT is contraindicated in women who have a known suspected history of estrogen-based cancer or known, suspected, or history of breast cancer, another non-hormonal therapy would meet an unmet medical need for patients who may not tolerate other drugs.

4. Benefit Assessment

The applicant submitted 2 clinical studies, Study 2693-CL-0301 (NCT 04003155) and Study 2693-CL-0302 (NCT 04003142) in support of efficacy for this application. Both trials were randomized, placebo-controlled, and included a 12-week double-blind period followed by an active treatment extension period (double-blind without a placebo control) for 40 weeks, for a total of 52 weeks. Participants, who were women ages 40 – 65 who were in clinically or hormonally-confirmed menopause, had moderate to severe VMS, and experienced a minimum of 7-8 moderate to severe VMS daily within the 10 days prior to randomization. Participants were randomized 1:1:1 to fezolinetant 30 mg daily, fezolinetant 45 mg daily, or placebo and stratified by smoking status (current smoker or never/former smoker). Both studies enrolled participants throughout the US, Canada, and Europe. In Study 301, 527 participants were randomized, and in Study 302, 501 participants were randomized. After 12 weeks, participants taking placebo were randomized again to fezolinetant 30 mg or 45 mg daily. If patients were initially treated with 30 mg or 45 mg fezolinetant, they used that dose again for the next 40 weeks.

The co-primary endpoints of both Studies 301 and 302 was the mean change in the frequency and severity of moderate to severe VMS at Weeks 4 and 12 of study. The persistence of effect was measured at 24 weeks to assess long-term efficacy was measured at Weeks 24 and 52.[d] The results for the co-primary endpoints in Studies 301 and 302 are as follows:

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 1. Study 2693-CL-0301: Change from Baseline in Mean Frequency and Severity of Moderate to Severe Vasomotor Symptoms Over 24 Hours

	Trial 2693-CL-0301		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	175	173	174
Mean Severity (SD)	2.43 (0.35)	2.39 (0.34)	2.40 (0.35)
Mean Frequency (SD)	10.51 (3.79)	10.65 (4.73)	10.44 (3.92)
Week 4 (N)	166	157	164
Mean Severity Change (SD)	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)
LS Mean (SE)	-0.27 (0.04)	-0.42 (0.04)	-0.46 (0.04)
Mean Frequency Change (SD)	-3.27 (4.18)	-5.35 (5.57)	-5.20 (4.07)
LS Mean	-3.32 (0.29)	-5.19 (0.30)	-5.39 (0.30)
Week 12 (N)	139	131	146
Mean Severity Change (SD)	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)
LS Mean	-0.37 (0.05)	-0.60 (0.05)	-0.57 (0.05)
Mean Frequency Change (SD)	-3.67 (4.18)	-6.44 (6.15)	-6.38 (4.48)
LS Mean	-3.90 (0.31)	-6.28 (0.32)	-6.44 (0.31)

Source: Adapted from Clinical Review, November 23, 2022

Table 2. Study 2693-CL-0302: Change from Baseline in Mean Frequency and Severity of Moderate to Severe Vasomotor Symptoms Over 24 Hours

	Trial 2693-CL-0302		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	167	166	167
Mean Severity (SD)	2.41 (0.32)	2.44 (0.33)	2.41 (0.34)
Mean Frequency (SD)	11.59 (5.02)	11.23 (4.88)	11.79 (8.26)
Week 4 (N)	151	155	155
Mean Severity Change (SD)	-0.31 (0.48)	-0.47 (0.58)	-0.61 (0.63)
LS Mean (SE)	-0.32 (0.05)	-0.47 (0.05)	0.61 (0.05)
Mean Frequency Change (SD)	-3.64 (4.15)	-5.52 (4.23)	-6.24 (4.78)
LS Mean	-3.72 (0.33)	-5.53 (0.33)	-6.26 (0.33)
Week 12 (N)	140	133	145
Mean Severity Change (SD)	-0.46 (0.65)	-0.60 (0.75)	-0.74 (0.71)
LS Mean	-0.48 (0.06)	-0.64 (0.06)	-0.77 (0.06)
Mean Frequency Change (SD)	-4.57 (5.14)	-6.43 (4.77)	-7.43 (6.47)
LS Mean	-4.97 (0.39)	-6.83 (0.39)	-7.50 (0.39)

Source: Adapted from Clinical Review, November 23, 2022

Participants who were treated with both 30 mg and 45 mg daily fezolinetant had statistically significant reductions from baseline in the severity and frequency of VMS symptoms at Weeks 4 and 12 of study 301 and 302.

In addition to the co-primary endpoints, the Agency conveyed to the applicant that the product also needed to demonstrate a clinically meaningful reduction of 2 moderate to severe vasomotor symptoms per day or 14 per week above placebo. This result should be obtained by Week 4 and maintained at Week 12 of study. In Study 301, fezolinetant 30 mg daily achieved this by Week 5 and maintained the effect through Week 12, while fezolinetant 45 mg daily achieved the clinically meaningful difference at

Week 4 and maintained through Week 12. In Study 302, fezolinetant 45 mg daily achieved this result at Week 4 and maintained through Week 12, while fezolinetant 30 mg daily did not achieve this result.

The clinical reviewers state in the clinical review of fezolinetant that based upon the evidence of efficacy, fezolinetant 45 mg daily should be approved as this dose achieved the co-primary efficacy endpoints and demonstrated a clinically meaningful threshold difference in the frequency of hot flashes at Week 4 and maintained that efficacy at Week 12.[13] While the applicant included results from the 30 mg daily fezolinetant dose, only the 45 mg dose was recommended for approval.

5. Risk Assessment & Safe-Use Conditions

The applicant used safety data from the two Phase 3 trials listed in Section 4, as well as the 52-week, randomized, placebo-controlled, double-blind, parallel-group, long term safety Study 2693-CL-0304 (NCT 04003389). This study randomized 1831 participants in the US, Canada, and Europe to placebo, fezolinetant 30 mg daily, and fezolinetant 45 mg daily in 1:1:1 ratio for the entire 52-week study.[e]

In the polled analysis of initial 12-week study period of all 3 trials, 33 treatment emergent adverse events (TEAEs) occurred. In the 52-week study period, 38 subjects reported a total of 50 TEAEs, the most common (> 3% of subjects experienced) of which were headache, liver function test increased, COVID 19, urinary tract infection, back pain, insomnia, and abdominal pain. Dose dependent increases in blood creatinine phosphokinase were seen, but most were mild and spontaneously resolved. One case of rhabdomyolysis required drug discontinuation but was a recurrence following new onset of a CrossFit program by the subject.

Drug-induced liver injury (DILI) was identified as a potential safety concern in Phase 2 studies. As a result, DILI analyses were performed throughout all Phase 3 studies. The clinical team also reviewed an unanticipated imbalance of the incidence of malignancy between subjects taking fezolinetant versus placebo.

5.1. Deaths

Two deaths were reported in clinical trials, with both subjects taking fezolinetant. One subject in Study 302 was a passenger involved in a motorcycle accident and died instantly as a result. Both the clinical reviewers and the applicant categorized this event as not related to study treatment. One subject in Study 304 experienced a cardiac arrest and anoxic brain injury and died 2 days later. This patient had a past medical history of diabetes, hypertension, obesity, and smoking. The clinical reviewer notes that it

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

is not possible to determine if this death was drug-related, however that subject's past medical history were likely the major contributors to the death.[13]

5.2. Elevated Hepatic Transaminases

The Applicant used an independent Liver Safety Monitoring Panel (LSMP) to oversee the clinical program, as recommended by the Agency. The Division of Hepatology and Nutrition (DHN) drug-induced liver injury (DILI) Team was consulted to characterize the risk of hepatic transaminase elevations seen with fezolinetant. No Hy's Law cases were seen in the Phase 3 studies. The applicant's LSMP and the Agency's DILI Team reviewed 14 subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x the upper limit of normal (ULN). The DILI Team assessed six subjects as unlikely DILI, four as possible, and four as probable. Seven cases were assessed as probable DILI by the LSMP or DILI Team were further analyzed, and these seven subjects had predominantly hepatocellular injury by R-value (>5), and median onset was 56 days from start of fezolinetant, with a range of 14 – 250 days. It was also noted that many of the subjects' transaminase levels improved even while continuing fezolinetant. The risk of elevated liver transaminases will be addressed in labeling in the warnings and precautions, accompanied by instructions to the prescriber to check baseline and month 3, 6, and 9 of fezolinetant therapy, and at any point that patients exhibit symptoms of liver injury liver transaminase (for the first 9 months) as regular transaminase monitoring was recommended by the DILI Team's consult.[14]

6. Expected Postmarket Use

Fezolinetant is expected to be primarily prescribed by gynecologists and primary care providers currently prescribing therapies for the vasomotor symptoms of menopause. This prescribing population is likely familiar with monitoring therapies with regular bloodwork, and how to manage the risks of fezolinetant.

7. Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for fezolinetant beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of fezolinetant based on the efficacy and safety information currently available.

Vasomotor symptoms related to menopause affect a large population of women in the US, and the effects disrupt sleep, cause embarrassment, and disrupt activities of daily living for months to years. Fezolinetant offers another effective non-hormonal option to treat the moderate to severe vasomotor symptoms associated with menopause. DRM and DUOG considered the risks of hepatic transaminase elevation and potential malignancies and if a REMS was necessary to mitigate them.

The first safety concern associated with fezolinetant is the potential to elevate hepatic enzymes. While DILI was noted in several subjects in clinical trials, the subjects' elevated hepatic transaminases returned to normal levels with either interruption of fezolinetant therapy or with continued use, and there were no adverse sequalae. Proposed labeling for fezolinetant takes into account the recommendations from the DILI Team's review. The labeling lists hepatic transaminase elevations in warnings and precautions and recommends transaminase monitoring at baseline and at month 3, 6, and 9 of therapy as well as at any point patients experience symptoms of liver failure. Multiple products have instructions for monitoring for prescribers, and fezolinetant will employ the same strategy to mitigate risks. The CDER Medical Policy and Program Review Council (MPPRC) met on December 14, 2022, to discuss NDA 216578 including the need for a boxed warning (BW) or if risk mitigation labeling was necessary. The MPPRC was split on the need for a BW, but agreed that fezolinetant does not require a REMS to mitigate the risk of DILI.[15] At the time of this review, the review team is not currently recommending a BW and negotiations for enhanced pharmacovigilance to further characterize this risk in the postmarket population are underway.

Malignancies were not of concern based on the nonclinical and Phase 1 and 2 studies, however, a dose-dependent imbalance was initially seen in the incidence of malignancies in fezolinetant treated subjects versus subjects receiving placebo in the Phase 3 studies. In the 52-week exposure group, the exposure adjusted incidence rates for non-benign neoplasms were 0.2, 0.7, and 1.2 per 100 participant years in the placebo, fezolinetant 30mg daily, and fezolinetant 45 mg daily populations, respectively. Upon further analysis, the clinical reviewer noted that most cancers were "sporadically distributed without patterns related to duration of drug exposure, body system, and/or cancer type," and were "singular in nature and occurring in disparate systems and varied cancer types except for colon cancer (2 cases), squamous cell skin cancer (3 cases) and endometrial cancer (3 cases)." The clinical reviewer also states that eight of the sixteen malignancies seen in treatment arms of the studies were likely to be preexisting at enrollment, which brings the incidence rate of subjects in the treatment arms to within the normal background malignancy rate for females of menopausal age.[13] A January 23, 2023, review by the Division of Oncology 3, stated that there was "insufficient data to support a definitive conclusion of an increased risk of malignancy in patients who received fezolinetant." Follow-up information on subjects who experienced malignancies during studies and potential causation was sent in response to an Agency request, and the information submitted constituted a major amendment to the application.[16] A joint review by the Division of Epidemiology II and the Division of Pharmacovigilance II states that the assessment of the incidence of malignancies was limited by several factors, including a lack of source documentation of relevant risk factors, physical exam findings, laboratory and imaging study results, protocol deviations, past medical history underreporting, abnormal/nondiagnostic laboratory and pathologic studies at screening or early in the study, detection bias due to concurrent clinical conditions

or imaging studies performed for unrelated reasons, and finally, alternate established cancer risk factors. The reviewers concluded that "the evidence to implicate fezolinetant in the development of malignancy is weak, and any causal association between fezolinetant exposure and neoplasms could not be established based on data provided by the applicant."[17] Endometrial hyperplasia and carcinoma are listed in Section 14 of the label as they were seen in clinical trials of fezolinetant and a REMS is not necessary to mitigate this risk.

9. Conclusion & Recommendations

Based on the available data, DRM and DUOG agree that a REMS is not necessary to ensure the benefits of fezolinetant outweigh the risks, which will be managed via labeling. Should DUOG have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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15. Medical Policy and Program Review Council, Meeting Minutes, December 14, 2022.
16. Brewer, J., CDER Division of Oncology 3 Review of Fezolinetant, January 23, 2023, DARRTS ID # 5126140
17. Dores, G, Ajao, A., OSE Integrated Review from DPV II and DEPI II of Fezolinetant, April 26, 2023, DARRTS ID# 5164288.

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