1. NAME OF THE MEDICINAL PRODUCT

Veoza™ 45 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 45 mg of fezolinetant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, light red, film-coated tablets debossed with the Astellas logo and '645' on the same side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fezolinetant is a nonhormonal selective neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

4.2 Posology and method of administration

Posology
The recommended dose of fezolinetant is 45 mg once daily.

Special populations
Elderly
Clinical studies have not been conducted for safety and efficacy in women initiating fezolinetant treatment over 65 years of age.

Paediatric population
The safety and efficacy of fezolinetant in this population have not been established.

Renal impairment
No dose modification is recommended for individuals with mild (eGFR 60 to less than 90 mL/min/1.73 m^2) or moderate (eGFR 30 to less than 60 mL/min/1.73 m^2) renal impairment (see section 5.2).

Fezolinetant is not recommended for use in individuals with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment. Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2) and is not recommended for use in this population (see section 5.2).

Hepatic impairment
No dose modification is recommended for individuals with Child-Pugh Class A (mild) chronic hepatic impairment (see section 5.2).

Fezolinetant is not recommended for use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment. Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment (see section 5.2).

Method of administration
Fezolinetant should be administered orally once daily at about the same time each day with or without food, taken with liquids, and should be swallowed whole. Do not cut, crush, or chew tablets.

If a dose of fezolinetant is missed or not taken at the usual time, administer the missed dose as soon as possible, unless there is less than 12 hours before the next scheduled dose. Return to the regular schedule the following day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of moderate or strong CYP1A2 inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Hepatotoxicity
Across the three phase 3 studies, elevations in serum alanine aminotransferase (ALT) levels at least 3 times the upper limit of normal (ULN) occurred in 2.1% of women receiving fezolinetant compared to 0.8% of women receiving placebo. Elevations in serum aspartate aminotransferase (AST) levels at least 3 times the ULN occurred in 1.0% of women receiving fezolinetant compared to 0.4% of women receiving placebo (see section 4.8). ALT and/or AST elevations were not accompanied by an increase in bilirubin greater than 2 times the ULN with fezolinetant. Women with ALT or AST elevations were generally asymptomatic. Transaminase levels returned to pre-treatment levels or close to these without sequelae with dose continuation, and upon dose interruption, or discontinuation.

In the post-marketing setting, cases of serious but reversible hepatotoxicity have been reported within the first few weeks of treatment. Patients have experienced transaminase elevations (greater than 10 times the ULN) with concurrent elevations in bilirubin and/or alkaline phosphatase (ALP), sometimes associated with signs or symptoms such as fatigue, pruritus, jaundice, dark urine, or abdominal pain.

Evaluate hepatic function (ALT, AST, ALP, and bilirubin) before initiating therapy. Do not initiate fezolinetant if ALT or AST is equal to or exceeds 2 times the ULN or if the total bilirubin is elevated (e.g., equal to or exceeds 2 times the ULN).

Patients should discontinue fezolinetant immediately and seek medical attention, including hepatic laboratory tests, if they experience signs or symptoms that may suggest hepatotoxicity such as new onset fatigue, decreased appetite, nausea, vomiting, pruritus, jaundice, pale feces, dark urine, or abdominal pain.

Follow-up evaluation of hepatic function is recommended monthly for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement.

Discontinue fezolinetant if:

- transaminase elevations are greater than 5 times the ULN.
- transaminase elevations are greater than 3 times the ULN and the total bilirubin level is greater than 2 times the ULN.

Exclude alternative causes of hepatic laboratory test elevations.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on fezolinetant
CYP1A2 inhibitors
Fezolinetant is a substrate of CYP1A2. Concomitant use of fezolinetant with drugs that are moderate or strong inhibitors of CYP1A2 increase the plasma C_{max} and AUC of fezolinetant (see section 5.2).

Concomitant use of moderate or strong CYP1A2 inhibitors with fezolinetant is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of fezolinetant in pregnant women is not recommended. There are no data on the use of fezolinetant in pregnant women.

In embryo-fetal toxicity animal studies with fezolinetant, embryo-lethality occurred at high doses above the human therapeutic dose in rats and rabbits, but no teratogenicity was observed (see section 5.3).

Breast-feeding
The use of fezolinetant in breast-feeding women is not recommended. There are no data to assess the effects of fezolinetant on the breastfed child or the effects on milk production. It is not known if fezolinetant is present in human milk.

Following administration of radiolabeled fezolinetant to lactating rats, the radioactivity concentration in milk was higher than that in the plasma at all time points, indicating that fezolinetant-derived components transferred to the tissues in infant rats via breast milk.

Fertility
There are no data on the effect of fezolinetant on human fertility. In the fertility study in female rats, fezolinetant did not affect fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No formal studies on the effects of the ability to drive and use machines have been performed; however, fezolinetant is considered to have a negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of fezolinetant was evaluated in three phase 3 studies (SKYLIGHT 1, 2, and 4). SKYLIGHT 1 and 2 were 12-week, randomized, placebo-controlled, double-blind studies, followed by a 40-week extension treatment period in women with moderate to severe VMS associated with menopause. SKYLIGHT 4 was a 52-week, randomized, placebo-controlled, double-blind long-term safety study in women with VMS associated with menopause. A total of 2203 women were administered fezolinetant once daily.

Across the phase 3 studies, the most frequent adverse reactions (≥ 3%) with fezolinetant 45 mg were diarrhea and insomnia.

There were no serious adverse reactions reported at an incidence greater than 1% across the total study population.

The most frequent adverse reactions leading to discontinuation with fezolinetant 45 mg were alanine aminotransferase (ALT) increased (0.3%) and insomnia (0.2%).

Tabulated summary of adverse reactions
Adverse reactions observed during clinical studies and from spontaneous reporting are listed below by frequency category in each system organ class. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Table 1. Adverse reactions for fezolinetant 45 mg

MedDRA system organ class (SOC)	Adverse reaction (preferred term)	Frequency category	Frequency %
Gastrointestinal disorders	Diarrhea	Common	3.2%
	Abdominal pain	Common	1.8%
Psychiatric disorders	Insomnia	Common	3.0%
Hepatobiliary disorders	Alanine aminotransferase (ALT) increased	Common	2.8%
	Aspartate aminotransferase (AST) increased	Common	1.5%
	Hepatotoxicity[1]	Not known[2]	Not known[2]

Preferred term in MedDRA (v.23.0).

[1] See Description of selected adverse reactions section.

[2] Adverse reactions of an unknown frequency have been identified during post-approval use of fezolinetant. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Description of selected adverse reactions

Hepatotoxicity

Serious cases of hepatotoxicity in which ALT and/or AST elevations were accompanied by an increase in total bilirubin including symptoms have been reported post-marketing (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

The maximum tolerated dose was determined to be 900 mg. At 900 mg, headache, nausea, and paresthesia were observed. In the case of overdose, the individual should be closely monitored, and supportive treatment should be considered based on signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Fezolinetant is a nonhormonal selective NK3 receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center.

The thermoregulatory center in the hypothalamus is innervated by KNDy neurons, which are inhibited by estrogen and stimulated by the neuropeptide NKB. Through the menopausal transition, declining estrogen disrupts the balance with NKB. Unopposed, NKB signaling increases KNDy neuronal activity leading to hypertrophy of the KNDy neuron and altered activity on the thermoregulatory center, resulting in VMS, also known as hot flashes and night sweats.

Pharmacodynamic effects

Fezolinetant treatment provided relief from VMS over 24 hours. Fezolinetant is not a hormone and treatment with fezolinetant did not show any clear trends or clinically relevant changes in sex hormones measured (follicle-stimulating hormone, testosterone, estrogen, and dehydroepiandrosterone sulfate) in menopausal women. Transient decrease of luteinizing hormone (LH) levels was observed at peak concentrations of fezolinetant.

Cardiac electrophysiology

A model-based approach was conducted to assess the QT prolongation risk of fezolinetant. No clinically relevant prolongation of QTc interval was predicted by the model at the therapeutic or supratherapeutic concentrations.

Clinical efficacy and safety

SKYLIGHT 1 (2693-CL-0301) and SKYLIGHT 2 (2693-CL-0302) studies

Efficacy: Effects on VMS

The efficacy of fezolinetant was evaluated in 1022 women with moderate to severe VMS associated with menopause in two 12-week, randomized, placebo-controlled, double-blind phase 3 studies, followed by a 40-week extension treatment period. The mean age was 54 years and women were Caucasian (81%), Black (17%), Asian (1%), and Hispanic/Latina (24%) ethnicity. Women who had a minimum average of 7 moderate to severe VMS per day were enrolled in the studies.

The study population included menopausal women with prior hormone replacement therapy (HRT) use (19.9%), with oophorectomy (21.6%), or with hysterectomy (32.1%).

The co-primary efficacy endpoints for both studies were the change from baseline in moderate to severe VMS frequency and severity to weeks 4 and 12. Data from the studies showed a statistically significant and clinically meaningful (≥ 2 hot flashes per 24 hours) reduction from baseline in the frequency of moderate to severe VMS to weeks 4 and 12 for fezolinetant 45 mg compared to placebo. Data from the studies showed a statistically significant reduction from baseline in the severity of moderate to severe VMS to weeks 4 and 12 for fezolinetant 45 mg compared to placebo.

A significantly higher proportion of women achieved a clinically meaningful within-subject reduction in the frequency of moderate to severe VMS at weeks 4 and 12 in the fezolinetant 45 mg group (46.6% week 4 and 47.2% week 12) than those in the placebo group (24.0% week 4 and 25.7% week 12) based on a pre-specified analysis for women who had at least a moderate improvement on the PGI-C VMS measure as the primary anchor.

Fezolinetant is efficacious across a wide range of women, irrespective of age, race, ethnicity, body mass index (BMI), and smoking status. Furthermore, the efficacy of fezolinetant is observed regardless of VMS frequency, severity, duration at baseline or time since amenorrhea, prior medical history of sleep disturbance, or prior medical history of hypertension. In addition, fezolinetant is efficacious in women with or without hysterectomy or oophorectomy, with or without prior HRT, and with or without concurrent use of serotonin reuptake inhibitor (SSRI).

Fezolinetant 45 mg reduced the frequency and severity of VMS within week one. Improvement in VMS frequency and severity was sustained throughout the 52-week studies.

Women initially on placebo and subsequently re-randomized to fezolinetant during the extension period experienced a reduction in frequency and severity of VMS consistent with that in women receiving fezolinetant throughout the studies.

Results of the co-primary endpoint for change from baseline to weeks 4 and 12 in mean frequency of moderate to severe VMS per 24 hours from SKYLIGHT 1 and 2 and from pooled studies are shown in Table 2.

Table 2. SKYLIGHT 1 and 2: Mean baseline and change from baseline in mean frequency of moderate to severe VMS per 24 hours to weeks 4 and 12

Parameter	SKYLIGHT 1		SKYLIGHT 2		Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=174)	Placebo (n=175)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	Fezolinetant 45 mg (n=341)	Placebo (n=342)
Baseline						
Mean (SD)	10.44 (3.92)	10.51 (3.79)	11.79 (8.26)	11.59 (5.02)	11.10 (6.45)	11.04 (4.46)
Change from baseline to week 4						
LS Mean (SE)	-5.39 (0.30)	-3.32 (0.29)	-6.26 (0.33)	-3.72 (0.33)	-5.79 (0.23)	-3.51 (0.22)
Mean % Reduction[2]	50.63%	30.46%	55.16%	33.60%	52.84%	31.96%
Difference vs Placebo (SE)	-2.07 (0.42)	--	-2.55 (0.46)	--	-2.28 (0.32)	--
P-value	< 0.001[1]	--	< 0.001[1]	--	< 0.001	--
Change from baseline to week 12						
LS Mean (SE)	-6.44 (0.31)	-3.90 (0.31)	-7.50 (0.39)	-4.97 (0.39)	-6.94 (0.25)	-4.43 (0.25)
Mean % Reduction[2]	61.35%	34.97%	64.27%	45.35%	62.80%	40.18%
Difference vs Placebo (SE)	-2.55 (0.43)	--	-2.53 (0.55)	--	-2.51 (0.35)	--
P-value	< 0.001[1]	--	< 0.001[1]	--	< 0.001	--

[1] Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance;
SD: Standard Deviation; SE: Standard Error.

[2] Mean % Reduction is a descriptive statistic and not from the mixed model.

Figures 1 and 2 show the mean frequency of moderate to severe VMS per 24 hours in SKYLIGHT 1 and 2.

Figure 1. SKYLIGHT 1: Mean (SE) frequency of moderate to severe VMS per 24 hours by week

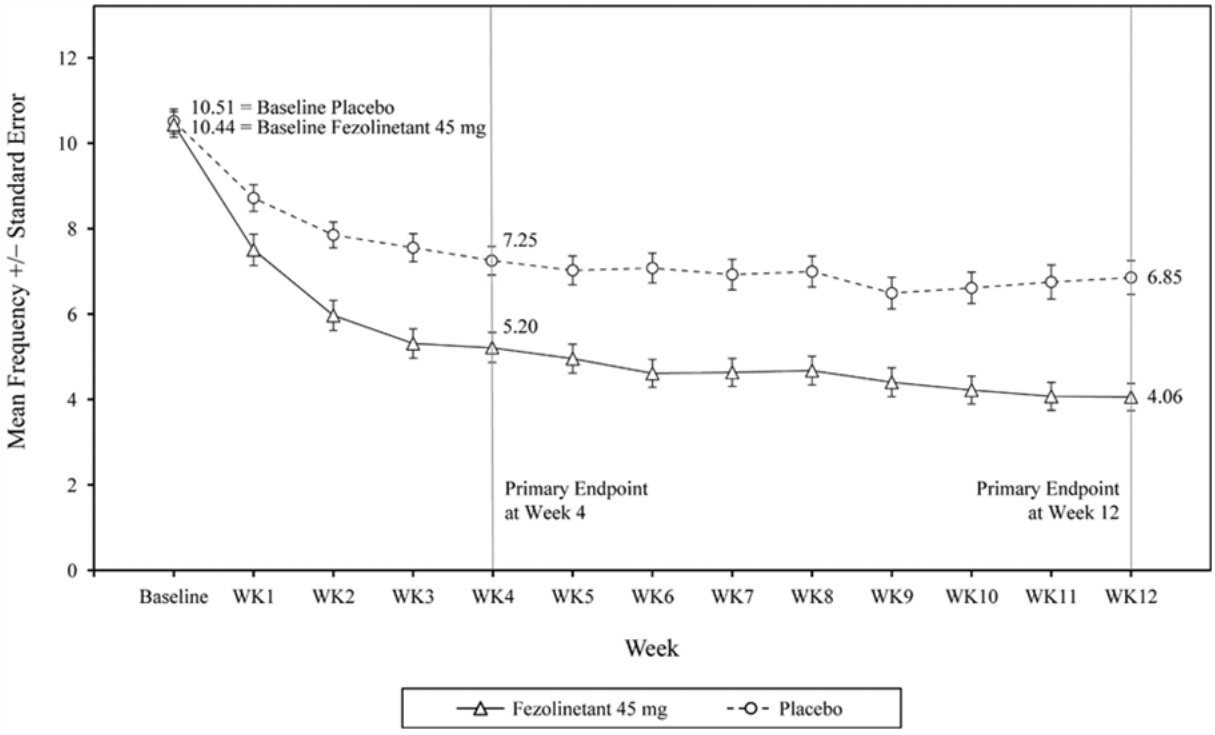
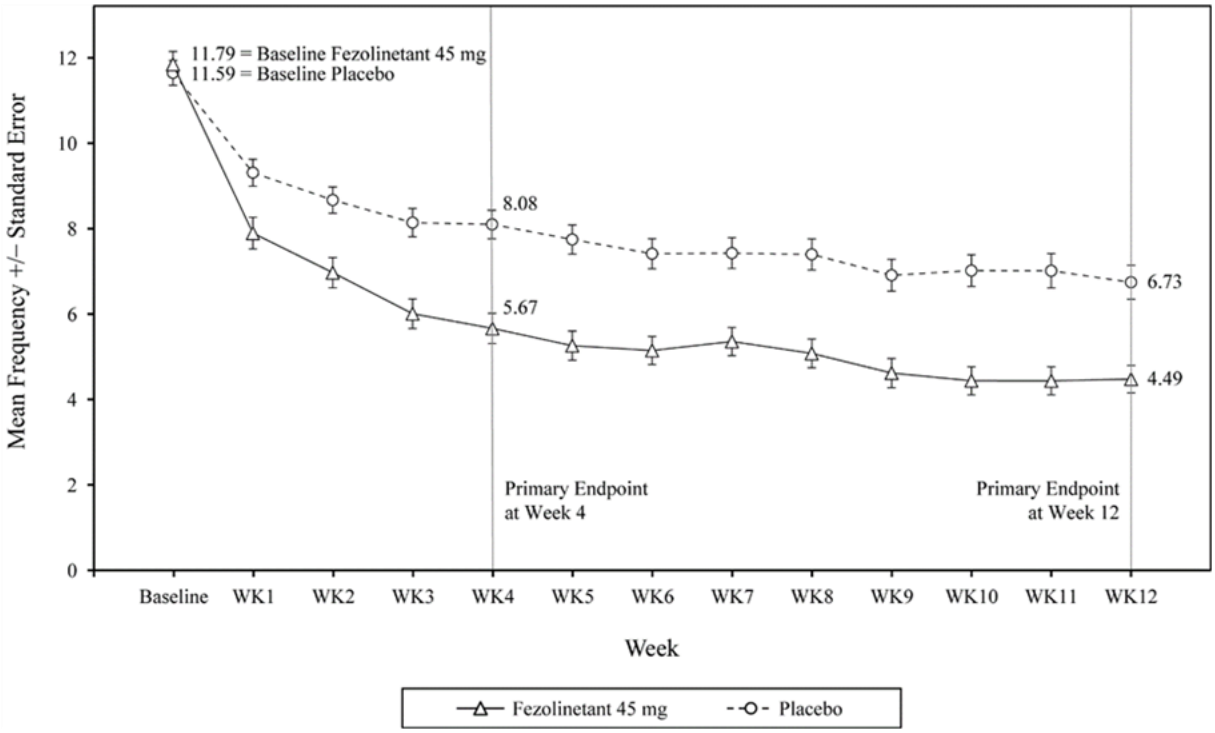


Figure 2. SKYLIGHT 2: Mean (SE) frequency of moderate to severe VMS per 24 hours by week



Results of the co-primary endpoint for change from baseline to weeks 4 and 12 in mean severity of moderate to severe VMS per 24 hours from SKYLIGHT 1 and 2 and from pooled studies are shown in Table 3.

Table 3. SKYLIGHT 1 and 2: Mean baseline and change from baseline in mean severity of moderate to severe VMS per 24 hours to weeks 4 and 12

Parameter	SKYLIGHT 1		SKYLIGHT 2		Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=174)	Placebo (n=175)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	Fezolinetant 45 mg (n=341)	Placebo (n=342)
Baseline						
Mean (SD)	2.40 (0.35)	2.43 (0.35)	2.41 (0.34)	2.41 (0.32)	2.40 (0.35)	2.42 (0.34)
Change from baseline to week 4						
LS Mean (SE)	-0.46 (0.04)	-0.27 (0.04)	-0.61 (0.05)	-0.32 (0.05)	-0.53 (0.03)	-0.30 (0.03)
Difference vs Placebo (SE)	-0.19 (0.06)	--	-0.29 (0.06)	--	-0.24 (0.04)	--
P-value	0.002[1]	--	< 0.001[1]	--	< 0.001	--
Change from baseline to week 12						
LS Mean (SE)	-0.57 (0.05)	-0.37 (0.05)	-0.77 (0.06)	-0.48 (0.06)	-0.67 (0.04)	-0.42 (0.04)
Difference vs Placebo (SE)	-0.20 (0.08)	--	-0.29 (0.08)	--	-0.24 (0.06)	--
P-value	0.007[1]	--	< 0.001[1]	--	< 0.001	--

[1] Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance;
SD: Standard Deviation; SE: Standard Error.

Other efficacy: Patient-reported outcomes

Sleep disturbance (PROMIS SD SF 8b)

Pooled efficacy analysis (SKYLIGHT 1 and 2) of the key secondary endpoint resulted in fezolinetant 45 mg demonstrating an improvement from baseline to week 12 (LS mean difference (SE): -1.5 (0.5), 95% CI: (-2.5, -0.5), nominal P-value: 0.004) in sleep disturbance compared to placebo, measured by the patient-reported outcomes measurement information system (PROMIS) Sleep Disturbance Short Form 8b Total Score. A reduction in PROMIS SD 8b was maintained through 52 weeks.

Menopause-specific quality-of-life (MENQoL)
Fezolinetant 45 mg resulted in an improvement from baseline to week 12 in health-related quality-of-life (HRQoL) compared to placebo, measured by the MENQoL total score and the VMS domain score of MENQoL. Reductions in MENQoL were maintained through 52 weeks. Results are shown in Table 4.

Table 4. SKYLIGHT 1 and 2: Mean baseline and change from baseline in total score and VMS domain score of MENQoL to week 12

Parameter	Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=341)	**Placebo (n=342)**
Total score		
Baseline mean (SD)	4.3 (1.4)	4.3 (1.4)
Mean (SD) change from baseline to week 12[1]	-1.3 (1.4)	-0.9 (1.4)
LS mean difference (SE) at week 12[2]	-0.5 (0.1)	--
95% CI	-0.7, -0.3	--
P-value[3]	< 0.001	--
VMS domain score		
Baseline mean (SD)	6.5 (1.6)	6.5 (1.4)
Mean (SD) change from baseline to week 12[1]	-2.4 (2.1)	-1.6 (2.0)
LS mean difference (SE) at week 12[2]	-0.9 (0.2)	--
95% CI	-1.2, -0.6	--
P-value[3]	< 0.001	--

[1] A negative change indicates a reduction/improvement from baseline.
[2] Differences are calculated by subtracting the LS mean of the placebo group from the LS mean of the fezolinetant group. LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance; SD: Standard Deviation; SE: Standard Error; CI: Confidence Interval.
[3] Multiplicity unadjusted P-value.

Safety: Endometrial safety
The long-term safety study (SKYLIGHT 4, study 2693-CL-0304) assessed safety and tolerability of fezolinetant in a total of 1830 women. The mean age was 55 years and women were Caucasian (80%), Black (17%), Asian (2%), and Hispanic/Latina (20%) ethnicity. The mean duration of exposure was 296 days. Endometrial safety was assessed by transvaginal ultrasound and endometrial biopsies in women who had baseline and post-baseline endometrial biopsies.

In SKYLIGHT 4, fezolinetant demonstrated no effect on the primary endpoints of endometrial hyperplasia or endometrial malignancy as assessed by endometrial biopsies. Fezolinetant had no effect on endometrial thickness as assessed by transvaginal ultrasound compared to placebo.

In the fezolinetant 45 mg dose group across the phase 3 studies (SKYLIGHT 1, 2, and 4), endometrial biopsy assessments identified 1 case of endometrial hyperplasia and no cases of endometrial malignancy. The rate of these events in the fezolinetant 45 mg dose group were ≤ 1% with the upper bound of the one-sided 95% confidence limit being ≤ 4% and met the pre-specified criteria for endometrial safety.

5.2 Pharmacokinetic properties

In healthy women, fezolinetant C_{max} and AUC increased proportionally with doses between 20 and 60 mg once daily.

After once-a-day dosing, steady-state plasma concentrations of fezolinetant were generally reached by day 2, with minimal fezolinetant accumulation. The pharmacokinetics of fezolinetant do not change over time.

Absorption
Fezolinetant C_{max} is usually achieved at 1 to 4 hours post-dose.

Effect of food
Fezolinetant may be administered with or without food. No clinically significant differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal.

Distribution
The mean apparent volume of distribution (V_z/F) of fezolinetant is 189 L. The plasma protein binding of fezolinetant is low (51%). The distribution of fezolinetant into red blood cells is almost equal to plasma.

Biotransformation
Fezolinetant is primarily metabolized by CYP1A2 in humans to yield oxidized major metabolite ES259564. ES259564 is approximately 20-fold less potent against human NK3 receptor with no significant off-target activities. The metabolite-to-parent ratio ranges from 0.7 to 1.8.

Elimination
The apparent clearance at steady-state of fezolinetant is 10.8 L/h. Following oral administration, fezolinetant is mainly eliminated in urine (76.9%) and to a lesser extent in feces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as ES259564. The effective half-life ($t_{1/2}$) of fezolinetant is 9.6 hours in women with VMS.

Special populations
Effects of age, race, and body weight
There are no clinically relevant effects of age (18 to 65 years), race (Black, Asian, Other), body weight (42 to 126 kg), or menopause status on the pharmacokinetics of fezolinetant.

Renal impairment
Following single-dose administration of 30 mg fezolinetant, there was no clinically relevant effect on fezolinetant exposure (C_{max} and AUC) in women with mild (eGFR 60 to less than 90 mL/min/1.73 m^2) to severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment. The AUC of ES259564 was not changed in women with mild renal impairment but increased approximately 1.7- to 4.8-fold in moderate (eGFR 30 to less than 60 mL/min/1.73 m^2) and severe renal impairment. Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2).

Hepatic impairment
Following single-dose administration of 30 mg fezolinetant in women with Child-Pugh Class A (mild) chronic hepatic impairment, mean fezolinetant C_{max} increased by 1.2-fold and AUC_{inf} increased by 1.6-fold, relative to women with normal hepatic function. In women with Child-Pugh Class B (moderate) chronic hepatic impairment, mean fezolinetant C_{max} decreased by 15% and AUC_{inf} increased by 2-fold. The C_{max} of ES259564 decreased in both mild and moderate chronic hepatic impairment groups while AUC_{inf} and AUC_{last} slightly increased less than 1.2-fold. Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment.

Pharmacologically induced menopause
Fezolinetant has not been studied in individuals with VMS induced by pharmacologic treatment of malignancy (e.g., breast cancer).

Drug-drug interactions
Clinical studies
Strong CYP1A2 inhibitors
Co-administration with fluvoxamine, a strong CYP1A2 inhibitor, resulted in an overall 1.8-fold increase in fezolinetant C_{max} and 9.4-fold increase in AUC; no change in t_{max} was observed.

Moderate CYP1A2 inducers
Smoking (moderate inducer of CYP1A2) decreased fezolinetant C_{max} to a geometric LS mean ratio of 71.74%, while AUC decreased to a geometric LS mean ratio of 48.29%. Smoking does not cause any clinically significant differences in fezolinetant efficacy.

Physiologically-based pharmacokinetic modeling predictions

Weak and moderate CYP1A2 inhibitors

Based on physiologically-based pharmacokinetic modeling, a typical weak CYP1A2 inhibitor (cimetidine; 300 mg every 6 hours) is predicted to increase the fezolinetant C_{max} by 1.3-fold and the AUC by 2-fold. A typical moderate CYP1A2 inhibitor (mexiletine; 400 mg every 8 hours) is predicted to increase the fezolinetant C_{max} by 1.4-fold and the AUC by 4.6-fold.

In vitro studies

Cytochrome P450 (CYP) enzymes

Fezolinetant is primarily metabolized by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19. Fezolinetant and ES259564 are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Fezolinetant and ES259564 are not inducers of CYP1A2, CYP2B6, and CYP3A4.

Transporters

Fezolinetant is not a substrate nor an inhibitor of P-glycoprotein (P-gp). ES259564 is a substrate of P-gp, but not an inhibitor of P-gp.

Both fezolinetant and ES259564 are not a substrate of BCRP, OATP1B1, and OATP1B3. In addition, ES259564 is not a substrate of OAT1, OAT3, OCT2, MATE1, and MATE2-K.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

An increase in the incidence of thyroid follicular cell adenoma was noted in the 2-year rat carcinogenicity study (186-fold the AUC_{24} at the human therapeutic dose of 45 mg). The increase is considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and, therefore, does not constitute a clinical carcinogenic risk. In the 26-week carcinogenicity study in rasH2 transgenic mice, neoplasms were not induced (47-fold the AUC_{24} at the human therapeutic dose).

Fezolinetant and ES259564 showed no genotoxic potential in the bacterial reverse mutation test, chromosomal aberration test, or *in vivo* micronucleus test.

Fezolinetant had no effect on female fertility or early embryonic development up to 100 mg/kg/day in rats (143-fold the AUC_{24} at the human therapeutic dose).

In embryo-fetal development toxicity studies, embryo-lethality was noted at the AUC_{24} 128- and 174-fold higher than the AUC_{24} at the human therapeutic dose in rats and rabbits, respectively. Rabbits also showed increased late resorption and reduced fetal weight at 75 mg/kg/day (28-fold the AUC_{24} at the human therapeutic dose). The no observed adverse effect level (NOAEL) for embryo-fetal development was 50 mg/kg/day in rats and 45 mg/kg/day in rabbits (62- and 16-fold the AUC_{24} at the human therapeutic dose in rats and rabbits, respectively). Fezolinetant did not show teratogenic potential in either rats or rabbits.

In the pre- and post-natal development study in rats, the NOAEL for maternal and fetal toxicity was 30 mg/kg/day (36-fold the AUC_{24} at the human therapeutic dose) based on delayed parturition and embryo-lethality at 100 mg/kg/day. The NOAEL for F_1 generation development was determined to be 100 mg/kg/day for females (204-fold the AUC_{24} at the human therapeutic dose) and 10 mg/kg/day for males (11-fold the AUC_{24} at the human therapeutic dose). The F_1 male showed incomplete balanopreputial separation which may delay male reproductive maturation or affect fertility.

Animal toxicology and/or pharmacology
Mortality was observed at 300 mg/kg/day (197-fold the AUC_{24} at the human therapeutic dose of 45 mg) in the rat 4-week repeat dose toxicity study. Moribund animals showed lethargy, reduced activity, labored respiration and staggering gait, and body weight loss. No mortality was noted in 13- or 26-week repeat dose toxicity studies at doses up to 200 mg/kg/day (148-fold the AUC_{24} at the human therapeutic dose). In female rats, daily administration of fezolinetant for 26 weeks at doses equal to or greater than 30 mg/kg/day (56-fold the AUC_{24} at the human therapeutic dose) showed uterine atrophy and epithelial mucification of the vagina and cervix.

In cynomolgus monkeys, fezolinetant administration at a dose of 40 mg/kg/day for 39 weeks was associated with mortality in one animal (102-fold the AUC_{24} at the human therapeutic dose). The moribund animal showed acute hemorrhagic anemia and severe thrombocytopenia. Thrombocytopenia was also observed in one surviving animal at a dose of 40 mg/kg/day, but not in other animals. In female cynomolgus monkeys, daily administration of fezolinetant for 39 weeks at doses equal to or greater than 10 mg/kg/day (26-fold the AUC_{24} at the human therapeutic dose) showed reduced ovarian activity.

In the rat safety pharmacology study, constricted pupils were noted at doses equal to or greater than 125 mg/kg. Decreased activity, touch escape response, and grip strength, which were thought to be indicative of sedation, were noted at 250 mg/kg. These clinical signs were not apparent at 24 hours post-dose. These sedation-like effects were also confirmed in the 4- and 13-week repeated dose toxicity studies in rats. The NOAEL for sedation-like effects was 30 mg/kg/day and 60-fold the C_{max} at the human therapeutic dose. Conversely, no CNS findings, including sedation, were observed in cynomolgus monkeys (5-, 13-, and 39-week repeated dose studies) up to the highest dose (40 or 50 mg/kg/day, 67-fold the C_{max} at the human therapeutic dose).

Fezolinetant inhibited hERG current density with an IC_{50} value of 231.8 µmol/L (83074.8 ng/mL, 371-fold the C_{max} at the human therapeutic dose). The telemetry study in cynomolgus monkeys and the Langendorff study showed no effects on the cardiovascular system. These results indicate that fezolinetant has little or no cardiovascular effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, magnesium stearate, hypromellose, talc, polyethylene glycol (macrogol), titanium dioxide, and ferric oxide (iron oxide red)

6.2 Incompatibilities

None.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store in the original package until dispensed in order to protect from moisture and humidity.

Package type	Recommended storage conditions
Aluminum/aluminum blisters	Do not store above 30°C.

6.5 Nature and contents of container

10 film-coated tablets. (1-blister of 10 film-coated tablets).
30 film-coated tablets. (3-blisters of 10 film-coated tablets).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Swallow the tablet whole with liquids. Do not cut, crush, or chew the tablet before swallowing. Fezolinetant can be taken with or without food.

Keep this and all medications out of the reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Name and address of manufacturer

Astellas Pharma Inc.
Yaizu Technology Center
180 Ozumi, Yaizu-shi, Shizuoka
425-0072, Japan

Date of revision of the text

01 Aug 2025

For any enquiry, please write to pv.my@astellas.com