SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 (tablet).

Round, light red tablets (approximately 7 mm diameter × 3 mm thickness), debossed with the company logo and ‘645’ on the same side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Veoza is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 45 mg once daily.

Benefit of long-term treatment should be periodically assessed since the duration of VMS can vary by individual.

Missed dose

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

Elderly

Fezolinetant has not been studied for safety and efficacy in women initiating Veoza treatment over 65 years of age. No dose recommendation can be made for this population.

Hepatic impairment

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

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

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).

Veoza 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).

Paediatric population

There is no relevant use of Veoza in the paediatric population for the indication of moderate to severe VMS associated with menopause.

Method of administration

Veoza should be administered orally once daily at about the same time each day with or without food and taken with liquids. Tablets are to be swallowed whole and not broken, crushed, or chewed due to the absence of clinical data under these conditions.

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).
- Known or suspected pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Medical examination/consultation

Prior to the initiation or reinstitution of Veoza, a careful diagnosis should be made, and complete medical history (including family history) must be taken. During treatment, periodic check-ups must be carried out according to standard clinical practice.

Liver disease

Veoza is not recommended for use in individuals with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment. Women with active liver disease or Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment have not been included in the clinical efficacy and safety studies with fezolinetant (see section 4.2) and this information cannot be reliably extrapolated. The pharmacokinetics of fezolinetant has been studied in women with Child-Pugh Class A (mild) and B (moderate) chronic hepatic impairment (see section 5.2).

Drug-induced liver injury (DILI)

Elevations in serum alanine aminotransferase (ALT) levels and serum aspartate aminotransferase (AST) at least 3 times the upper limit of normal (ULN) were observed in women treated with fezolinetant, including serious cases with increased total bilirubin and symptoms suggesting liver injury. Elevated liver function tests (LFTs) and symptoms suggestive of liver injury were generally reversible on discontinuation of therapy. LFTs must be performed prior to treatment initiation with fezolinetant. Treatment should not be started if ALT or AST is ≥ 2 x ULN or if total bilirubin is elevated (e.g., ≥ 2 x ULN). LFTs must be performed monthly during the first three months of treatment, then based on clinical judgement. LFTs must also be performed when symptoms suggestive of liver injury occur.

Treatment should be discontinued in the following situations:
- Transaminase elevations are ≥ 3 x ULN with: total bilirubin > 2 x ULN OR symptoms of liver injury.
- Transaminase elevations > 5 x ULN.

Monitoring of liver function should be maintained until they have normalised. Patients should be informed about the signs and symptoms of liver injury and should be advised to contact their doctor immediately once these occur.

Known or previous breast cancer or oestrogen-dependent malignancies

Women undergoing oncologic treatment (e.g., chemotherapy, radiation therapy, anti-hormone therapy) for breast cancer or other oestrogen-dependent malignancies have not been included in the clinical studies. Therefore, Veoza is not recommended for use in this population as the safety and efficacy are unknown.

Women with previous breast cancer or other oestrogen-dependent malignancies and no longer on any oncologic treatment have not been included in the clinical studies. A decision to treat these women with Veoza should be based on a benefit-risk consideration for the individual.

Concomitant use of hormone replacement therapy with oestrogens (local vaginal preparations excluded)

Concomitant use of fezolinetant and hormone replacement therapy with oestrogens has not been studied, and therefore concomitant use is not recommended.

Seizures or other convulsive disorders

Fezolinetant has not been studied in women with a history of seizures or other convulsive disorders. There were no cases of seizures or convulsive disorders during clinical studies. A decision to treat these women with Veoza should be based on a benefit-risk consideration for the individual.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on fezolinetant

CYP1A2 inhibitors

Fezolinetant is primarily metabolised by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19. Concomitant use of fezolinetant with medicinal products that are moderate or strong inhibitors of CYP1A2 (e.g., ethinyl oestradiol containing contraceptives, mexiletine, enoxacin, fluvoxamine) increase the plasma C_{max} and AUC of fezolinetant.

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

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. Given the large effect of a strong CYP1A2 inhibitor and supportive modelling, the increase in fezolinetant concentrations is expected to be of clinical concern also following concomitant use with moderate CYP1A2 inhibitors

(see section 4.3). The increase in fezolinetant exposure was however not predicted to be clinically relevant following concomitant use with weak CYP1A2 inhibitors.

CYP1A2 inducers

In vivo data

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%. The efficacy data did not point to relevant differences between smokers and non-smokers. No dose modification is recommended for smokers.

Transporters

In vitro data

Fezolinetant is not a substrate of P-glycoprotein (P-gp). Major metabolite ES259564 is a substrate of P-gp.

Effect of fezolinetant on other medicinal products

Cytochrome P450 (CYP) enzymes

In vitro data

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

In vitro data

Fezolinetant and ES259564 are not inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2-K (IC_{50} > 70 µmol/l). Fezolinetant inhibited OAT1 and OAT3 with IC_{50} values of 18.9 µmol/l (30 × $C_{max,u}$) and 27.5 µmol/l (44 × $C_{max,u}$), respectively. ES259564 does not inhibit OAT1 and OAT3 (IC_{50} > 70 µmol/l).

4.6 Fertility, pregnancy and lactation

Pregnancy

Veoza is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during use with Veoza, treatment should be withdrawn immediately.

There are no or limited data from the use of fezolinetant in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Perimenopausal women of childbearing potential should use effective contraception. Non-hormonal contraceptives are recommended for this population.

Breast-feeding

Veoza is not indicated during lactation.

It is unknown whether fezolinetant and its metabolites are excreted in human milk. Available pharmacokinetic data in animals showed excretion of fezolinetant and/or its metabolites in animal milk (see section 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Veoza therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

Fezolinetant has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions with fezolinetant 45 mg were diarrhoea (3.2%) and insomnia (3.0%).

There were no serious adverse reactions reported at an incidence greater than 1% across the total study population. On fezolinetant 45 mg, four serious adverse reactions were reported. The most serious adverse reaction was an event of endometrial adenocarcinoma (0.1%).

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

Tabulated list of adverse reactions

The safety of fezolinetant has been studied in 2203 women with VMS associated with menopause receiving fezolinetant once daily in phase 3 clinical studies.

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)	Frequency category	Adverse reaction
Psychiatric disorders	Common	Insomnia
Gastrointestinal disorders	Common	Diarrhoea, Abdominal pain
Hepatobiliary disorders	Common	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased
	Not known	Drug-induced liver injury (DILI)*

*see Description of selected adverse reactions

Description of selected adverse reactions

ALT increased/AST increased/DILI
Serious cases with elevations of ALT and/or AST (> 10 x ULN) with concurrent elevations in bilirubin and/or alkaline phosphatase (ALP) were reported post-marketing. In some cases, elevated liver function tests were associated with signs and symptoms suggestive of liver injury such as fatigue, pruritus, jaundice, dark urine, pale faeces, nausea, vomiting, decreased appetite, and/or abdominal pain (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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Doses of fezolinetant up to 900 mg have been tested in clinical studies in healthy women. At 900 mg, headache, nausea, and paraesthesia 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

Pharmacotherapeutic group: Other gynaecologicals, other gynaecologicals, ATC code: G02CX06.

Mechanism of action

Fezolinetant is a non-hormonal selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron, which is postulated to restore the balance in KNDy neuronal activity in the thermoregulatory centre of the hypothalamus.

Pharmacodynamic effects

In postmenopausal women, with fezolinetant treatment, a transient decrease of luteinizing hormone (LH) levels was observed. No clear trends or clinically relevant changes in sex hormones measured (follicle-stimulating hormone (FSH), testosterone, oestrogen, and dehydroepiandrosterone sulphate) in postmenopausal women were observed.

Clinical efficacy and safety

Efficacy: Effects on VMS

The effects of fezolinetant were studied in postmenopausal women with moderate to severe VMS in two 12-week, randomised, placebo-controlled, double-blind phase 3 studies of identical design, followed by a 40-week extension treatment period (SKYLIGHT 1 – 2693-CL-0301 and SKYLIGHT 2 – 2693-CL-0302). Women who had a minimum average of 7 moderate to severe VMS per day were enrolled in the studies.

The study population included postmenopausal women defined as having amenorrhoea for ≥ 12 consecutive months (70.1%) or amenorrhoea for ≥ 6 months with FSH > 40 IU/l (4.1%) or having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit (16.1%).

The study population included postmenopausal women with one or more of the following: prior hormone replacement therapy (HRT) use (19.9%), prior oophorectomy (21.6%), or prior hysterectomy (32.1%).

In the studies, a total of 1022 postmenopausal women (81% Caucasian, 17% Black, 1% Asian, 24% Hispanic/Latina ethnicity, and aged ≥ 40 years and ≤ 65 years with an average age of 54 years) were randomised and stratified by smoking status (17% smokers).

The 4 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 as defined in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. Each study demonstrated 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.

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. Mean baseline and change from baseline to weeks 4 and 12 for mean frequency of moderate to severe VMS per 24 hours

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.

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. Mean baseline and change from baseline to weeks 4 and 12 for mean severity of moderate to severe VMS per 24 hours

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.

Safety: Endometrial safety

In the long-term safety data (SKYLIGHT 1, 2, and 4), endometrial safety of fezolinetant 45 mg was assessed by transvaginal ultrasound and endometrial biopsies (304 women had baseline and post-baseline endometrial biopsies during 52 weeks of treatment).

Endometrial biopsy assessments did not identify an increased risk of endometrial hyperplasia or malignancy according to pre-specified criteria for endometrial safety. Transvaginal ultrasound did not reveal increased endometrial thickness.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with fezolinetant in all subsets of the paediatric population for the treatment of moderate to severe VMS associated with menopause (see section 4.2 for information on paediatric use).

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. No clinically significant differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal. Veoza may be administered with or without food (see section 4.2).

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 metabolised by CYP1A2 to yield oxidised major metabolite ES259564. ES259564 is approximately 20-fold less potent against human NK3 receptor. 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 faeces (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, body weight, and menopause status

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

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.

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. Veoza is not recommended for use in women with severe renal impairment or with end-stage renal disease because of lack of long-term safety data in this population.

Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 ml/min/1.73 m^2).

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Repeated dose toxicity

Repeated administration of fezolinetant to rats and monkeys showed the effects consistent with the primary pharmacological action (oestrous cycle disruptions, the lack of ovarian activity, decreased uterine and/or ovarian weight, uterine atrophy). These effects were observed at high exposure levels (> 10-fold of the anticipated clinical exposure at the human therapeutic dose of 45 mg). Furthermore, in rats, secondary effects were seen on the liver and thyroid which are considered to be an adaptive response to the enzyme induction and in the absence of functional impairment and accompanying necrotic changes were considered non-adverse. The finding of thyroid follicular cell hyperplasia is considered secondary to the liver enzyme induction due to the increased thyroid hormone metabolism, resulting in the positive feedback to the pituitary for the stimulation of thyroid stimulating hormone production and increased thyroid activity. It is generally accepted that rodents are more sensitive to this type of liver-mediated thyroid toxicity than humans, thus these findings are not expected to be clinically relevant.

In monkeys, thrombocytopenia, sometimes associated with haemorrhagic episodes and regenerative anaemia, was seen following repeated administration at high dose levels (> 60-fold of human exposure at the human therapeutic dose).

Genotoxicity

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

Carcinogenicity

An increase in the incidence of thyroid follicular cell adenoma was noted in a 2-year rat carcinogenicity study (186-fold of human exposure at the human therapeutic dose). The increase is considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and does not constitute a clinical carcinogenic risk.

Additionally, increased incidence of thymomas, which slightly exceeded the historical control range, was observed in both species. However, these findings were only noted at exposure levels significantly in excess (> 50-fold) of the clinical exposure at the human therapeutic dose, and therefore are not expected to be relevant to humans.

Reproductive and developmental toxicity

Fezolinetant had no effect on female fertility or early embryonic development in the rat study at exposure levels of 143-fold of human exposure at the human therapeutic dose.

In embryo-foetal development toxicity studies, embryo-lethality was noted at the exposure levels of 128- and 174-fold at the human therapeutic dose in rats and rabbits, respectively. Rabbits also showed increased late resorption and reduced foetal weight at the exposure levels of 28-fold at the human therapeutic dose. Fezolinetant did not show teratogenic potential in either rats or rabbits. In the pre- and post-natal development study in rats, increased dose-responsive total litter loss/abortions was observed at the exposure levels of 36-fold of the anticipated clinical exposure at the maximum recommended human dose, while reduced sexual maturation in male

progeny was seen at the 204-fold exposure levels at the maximum recommended human dose.

Following administration of radiolabelled fezolinetant to lactating rats, the radioactivity concentration in milk was higher than that in the plasma at all time points, indicating excretion of fezolinetant and/or its metabolites in the breast milk.

Environmental risk assessment

Environmental risk assessment studies have shown that fezolinetant may pose a risk to the aquatic environment (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Mannitol (E421)

Hydroxypropyl cellulose (E463)

Low-substituted hydroxypropyl cellulose (E463a)

Microcrystalline cellulose (E460)

Magnesium stearate (E470b)

Film coating

Hypromellose (E464)

Talc (E553b)

Macrogol (E1521)

Titanium dioxide (E171)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PA/Aluminium/PVC/Aluminium unit dose blisters in cartons.

Pack sizes: 28 × 1, 30 × 1, and 100 × 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the aquatic environment (see section 5.3).

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

7 MARKETING AUTHORISATION HOLDER

Astellas Pharma Ltd.
300 Dashwood Lang Road
Bourne Business Park
Addlestone
United Kingdom
KT15 2NX

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00166/0437

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/12/2023

10 DATE OF REVISION OF THE TEXT

05/05/2026