swissmedic

Date: 19 June 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Veoza

International non-proprietary name:	fezolinetant
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	45 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Astellas Pharma AG
Marketing authorisation no.:	69232
Decision and decision date:	approved on 4 December 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DILI	Drug induced liver injury
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
HRT	Hormone replacement therapy
ICH	International Council for Harmonisation
INN	International non-proprietary name
KNDy	Kisspeptin / neurokinin B / dynorphin
LoQ	List of Questions
LSMP	Liver Safety Monitoring Panel
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
NK3	Neurokinin 3
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily (Latin: quaque die)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal
VMS	Vasomotor symptoms

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for fezolinetant in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia and Switzerland.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Fezolinetant is a non-hormonal, selective NK3 receptor antagonist indicated for the treatment of moderate to severe VMS associated with menopause.

2.2.2 Approved indication

Treatment of moderate to severe vasomotor symptoms (VMS) in postmenopausal patients.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Veoza is 45 mg once daily.
The benefit of long-term treatment should be assessed regularly, as the duration of VMS may vary from individual to individual.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	10 January 2023
Formal control completed	7 February 2023
List of Questions (LoQ)	7 June 2023
Response to LoQ	6 August 2023
Preliminary decision	20 September 2023

Response to preliminary decision	5 October 2023
Labelling corrections and/or other aspects	30 October 2023
Response to labelling corrections and/or other aspects	14 November 2023
Final decision	4 December 2023
Decision	approval

3 Medical context

Vasomotor symptoms (VMS, hot flushes) are common in women during and after menopause and are caused by decreasing oestrogen levels as ovarian function declines. Even if their prevalence (60-85% of all menopausal women) is highest during the first two years after menopause, VMS may last for up to a decade, with a “typical” duration of 7.4 years mentioned in the literature.

Both frequency and severity of menopausal VMS show considerable inter-individual variability. In Europe, the prevalence of moderate to severe VMS (as they constitute the indication for Veoza) is estimated at approx. 40%.

For several decades, hormone replacement therapy (HRT) with oestrogens, in non-hysterectomised women combined with a progestin, has been available for the treatment of symptoms of oestrogen deficiency and for prophylaxis of postmenopausal osteoporosis, and can be considered the gold standard for symptomatic treatment of bothersome VMS. However, HRT is associated with several relevant safety issues, in particular an increased risk for breast cancer, but also for thromboembolic events. As alternative approaches are rare, to date, a relevant number of symptomatic patients has remained untreated or not sufficiently treated, either because of contraindications for HRT or because the patient refuses hormonal treatment.

The pathomechanism of hot flushes remained unknown for a long time. In the 2010s, new data suggested that kisspeptin / neurokinin B / dynorphin (KNDy) neurons were involved in thermoregulation and hot flushes, which formed the basis for investigating neurokinin 3 (NK3) inhibitors in this indication. These substances can be considered a non-hormonal treatment.

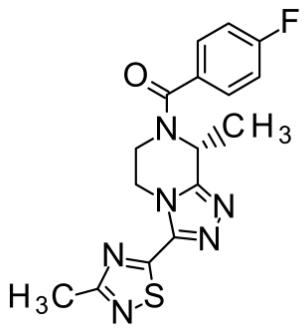
Neurokinin B is a member of the tachykinin family of peptides. Inactivating mutations in the tachykinin 3 or tachykinin 3 receptor gene are associated with pubertal failure and congenital hypogonadotropic hypogonadism in humans.

Fezolinetant is the first NK3 antagonist approved for the treatment of menopausal VMS.

4 Quality aspects

4.1 Drug substance

INN: Fezolinetant
Chemical name:
[(8R)-5,6-dihydro-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl](4-fluorophenyl)methanone;
(4-Fluorophenyl)[(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]methanone
Molecular formula: $C_{16}H_{15}FN_6OS$
Molecular mass: 358.39
Molecular structure:



Physico-chemical properties: Fezolinetant is a white powder or granular solid. It has one asymmetric centre and is manufactured as the R-enantiomer. Fezolinetant is highly soluble according to the biopharmaceutical classification system. Two polymorphic forms have been identified. The manufacturing process consistently produces the same polymorphic form. Fezolinetant is non-hygroscopic.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is monitored with appropriate in-process controls and tests for isolated intermediates.

Specification: The structure of fezolinetant has been elucidated using several spectroscopic techniques. To ensure a consistent quality, the specifications include the relevant test parameters as described in the current guidelines. Analytical methods have been described and validated according to ICH requirements.

Stability: The bulk drug substance is packaged in double polyethylene bags and then placed in a rigid container. Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Description and composition: The drug product is an immediate-release dosage form for oral administration. Veoza 45 mg tablets are round, light red film-coated tablets (approximately 7.1 mm diameter) debossed with the company logo and 645 on the same side. All excipients are widely used in pharmaceutical solid oral dosage forms. They meet the standards defined in the current Ph. Eur. with the exception of iron oxide red (film coat), which complies with the relevant standards for food additives.

Pharmaceutical development: Capsules were used for phase 1 and phase 2 clinical studies. Film-coated tablets were used for phase 3 clinical studies and were compared to the early phase capsules in a relative bioavailability study. Film-coated tablets with the intended commercial formulation were compared to the phase 3 tablets in a bioequivalence study.

Manufacture: The drug product is manufactured by a standard manufacturing process, which includes milling, dissolving, wet granulation, blending, tabletting and film-coating steps. Process parameters and in-process controls are defined. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life are established. The specifications include the parameters description (visual), identity tests, assay (liquid chromatography (LC)), degradation products (LC), dissolution, uniformity of dosage units (Ph. Eur.) and microbial limits (Ph.Eur.). The analytical procedures are adequately described, and non-compendial methods are validated according to the current ICH requirements. Batch analysis data have been provided. The results are within the specifications and consistent from batch to batch.

Container Closure System: Satisfactory information on the proposed container closure system has been provided. The drug product is packaged in aluminium-aluminium blisters.

Stability: Appropriate stability data have been generated following the relevant (ICH) guidelines. Based on the stability studies, appropriate shelf-life and storage conditions were established.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Swissmedic has not assessed the data relating to the non-clinical aspects of this application, but peer-reviewed and hence is adopting the results of the assessment of the foreign reference authority (see section on Applicant's request/Work-sharing procedure).

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption

Following oral administration, fezolinetant is rapidly absorbed, with median T_{max} values ranging from 1 to 4 h. For the main metabolite ES259564, T_{max} is generally achieved with a 1-h delay compared to the T_{max} of the parent compound fezolinetant.

An absolute bioavailability study was not conducted. Data from a mass balance study suggest a high absolute fezolinetant bioavailability with a urinary recovery of radioactivity of 76.9% (based on collection intervals up to 144 h). In addition, the in vitro permeability study 2693-ME-0011 indicates a high fezolinetant permeability in Caco-2 cell assays.

The effect of food (high-calorie, high-fat) on the PK of fezolinetant is modest, with a 0.5-h delay in median T_{max} in the fed vs. the fasted state and a corresponding 23 % decrease in C_{max} with no meaningful change in AUC. As a consequence, the Phase III studies were conducted regardless of food intake, which is also the intake recommendation in the proposed label.

Pharmacokinetics after multiple dosing

Following once daily administration of the proposed fezolinetant dose of 45 mg, steady state is generally reached on day 2 of dosing with fezolinetant steady-state C_{max} and $AUC_{0\text{-}tau}$ values of 458 ng/ml and 3855 ng*h/ml, respectively, with minimal accumulation (20 to 30%) given the 24-h dosing and the fezolinetant elimination half-life and an absence of time-dependent fezolinetant PK (i.e. no fezolinetant-mediated auto-induction or inhibition).

Dose proportionality

Fezolinetant dose proportionality was investigated across a wide range of doses (20 to 720 mg) following multiple doses in female subjects. Increases in fezolinetant C_{max} were dose proportional with slightly more than proportional increases in $AUC_{0\text{-}tau}$. In the narrower clinically relevant dose range of 20 to 60 mg given once daily (QD), dose proportionality was observed for both C_{max} and AUC_{tau} in female participants.

Distribution

Plasma protein binding of fezolinetant is low with values ranging from 50.2% to 52.4% at concentrations of 0.2, 5 and 100 µg/ml in human plasma. The volume of distribution at steady state (V_{ss}/F) was calculated to be 189 L (based on the pivotal popPK analysis).

Metabolism

Fezolinetant is metabolised via CYP1A2 to form the main plasma metabolite ES259564, which is generated following the oxidation of methyl group in the methylthiadiazole ring. In the mass balance study, the metabolite ES259564 $AUC_{0\text{-}tlast}$ was approximately twice the parent AUC. No other fezolinetant metabolites were identified in plasma.

Elimination

A mass balance study indicated that renal excretion is the predominant excretion route (76.9% of the radioactive dose). With a 14.0% faecal excretion the total radioactive recovery is 90.9% (data are based on the measured collection intervals up to 144 h).

In urine, ES259564 is the most abundant entity accounting for approximately 55% of the administered dose. Further urinary metabolites were identified at low levels (M1: 2.5%, M4: 3.7%, M5: 6.1% and M6: 1.5% of the administered dose). Unchanged fezolinetant in urine accounted for approximately 1% of the administered dose.

In faeces the metabolite M4 was the most abundant moiety at 7.4% of the dose, while ES259564 accounted for 1.9% with trace amounts of unchanged fezolinetant (0.1% of the administered dose). Further metabolites recovered in faeces were M1, which accounted for 1%, while four unidentified metabolites accounted for 0.6 % of the administered dose or less.

The elimination half-life for fezolinetant was calculated to be 9.6 h in a typical 70 kg, white, non-smoking female from Phase III studies based on a popPK analysis. The elimination half-life of ES259564 was, in general, 1 to 1.5 h longer than the respective values obtained for the parent in the individual studies.

Special populations/Intrinsic factors

Two dedicated studies were submitted in patients with impaired hepatic (mild and moderate impairment) and renal function (mild, moderate and severe impairment). Both studies were conducted as single-dose studies of 30 mg.

Hepatic impairment: Moderate fezolinetant exposure increases were observed for mild hepatic impairment (fezolinetant $AUC_{0\text{-tlast}}$ + 56%). For moderate impairment, a doubling (+ 94%) of the fezolinetant $AUC_{0\text{-tlast}}$ was observed. While fezolinetant may be given to patients with mild hepatic impairment without dose adjustment, the administration of fezolinetant to patients with moderate or severe hepatic impairment is contraindicated due to hepatotoxicity.

Renal impairment: While fezolinetant C_{max} remained unchanged, AUC was unexpectedly decreased (with the highest $AUC_{0\text{-t}}$ decrease of 31% and $AUC_{0\text{-inf}}$ decrease of 52% in the mild renal impairment group compared to the matched control). For metabolite ES259564, major and consistent increases in AUC were observed for moderate and severe renal impairment compared to the respective matched control (1.7-fold for moderate and 4.8-fold for severe renal impairment). ES259564 C_{max} values were increased 1.7-fold and 2.3-fold, respectively, in the moderate and severe renal impairment groups compared to matched controls. Based on these results and safety findings in the Phase III studies, a mild or moderate renal impairment does not warrant a fezolinetant dose adjustment, whereas administration of fezolinetant in patients with severe renal impairment and in patients with end-stage renal disease is contraindicated.

The impact of additional covariates was further investigated in popPK analyses.

The pivotal popPK analysis is based on fezolinetant concentration data from 14 studies (8 Phase I, 4 Phase II and 2 Phase III). A two-compartment model with first order elimination and complex absorption adequately described the fezolinetant concentration-time data from healthy women and women with VMS, uterine fibroids, or polycystic ovarian syndrome. The final model included 13,057 measurable fezolinetant concentrations from 1488 subjects. The dataset included female subjects with ages ranging from 19 to 65 years. 18 % and 3% of the population was African American and Asian, respectively. Approximately 14% of subjects were current smokers and approximately 10% were premenopausal women.

The following covariates were identified:

- **Smoking status**: 51% increase in Cl/F compared to non-smoking, which resulted in a 33.9% decrease in AUC_{ss} and 8.6% decrease in $C_{max\ ss}$.
- **Body weight**: High weight (100 kg): 17.2% decrease in C_{max}; low weight (55 kg): 25.6% increase in C_{max} compared to 70-kg standard female
- **Race (Black)**: 6.6% decrease in C_{max} compared to a standard Caucasian female
- **Asian (Chinese and Japanese combined) vs. non-Asian**: 23% increase in AUC and a 10% increase in C_{max}.

No fezolinetant dose adjustments are considered necessary based on age (19 – 65 years), ethnicity, smoking status or body weight.

Interactions

CYP enzymes: No direct and time-dependent inhibition of CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) up to concentrations of 125 µM of fezolinetant and ES259564 was shown. No significant induction of CYP1A2, CYP2B6 and CYP3A4 was demonstrated up to concentrations of 100 µM for fezolinetant and ES259564.

Transporters: Fezolinetant and ES259564 were not identified as clinically relevant substrates of P-gp, BCRP, OATP1B1, OATP1B3, OATP1A2 and OATP2B1. Fezolinetant and ES259564 were not identified as inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K.

PBPK analyses: Two PBPK reports were submitted to characterise the impact of weak and moderate CYP1A2 inhibitors on fezolinetant and the impact of fezolinetant on OAT1 / OAT 3 substrates.

To complement the result of the in vivo interaction study with the strong CYP1A2 inhibitor fluvoxamine (see below), the potential impact of a mild CYP1A2 inhibition by cimetidine, or of a moderate CYP1A2 inhibition by mexiletine was explored. As result of these investigations, the co-administration of CYP1A2 inhibitors (independent of strength) is contraindicated. For the OAT1 and OAT3 substrates no interaction was predicted based on the PBPK analyses.

In vivo data: The applicant submitted one clinical drug-drug interaction study to further characterise the in vivo interaction potential of fezolinetant. Co-administration of fluvoxamine resulted in an approximately 2-fold increase in fezolinetant C_{max} and in an approximately 10-fold increase in AUC by the strong CYP1A2 inhibition, and an increase in $T_{1/2}$ from 4 h (fezolinetant alone) vs. 22.4 h (co-administration of fluvoxamine). As the formation of the metabolite ES259564 is slowed, an approximately 80% reduction in ES259564 C_{max} was observed.

Pharmacodynamics

Fezolinetant is a non-hormonal selective antagonist of the NK3 receptor. It blocks binding of neurokinin B (NKB) to the kisspeptin / neurokinin B / dynorphin (commonly referred to as “KNDy”) neurons. Since the KNDy neurons express oestrogen receptor α (ERα) and NK3 receptors, the signalling of these KNDy neurons is balanced by negative feedback from oestrogen/ERα signalling and positive stimulation from NKB/NK3 signalling. In oestrogen-deficient states, such as in the menopause, this balance is compromised and, as a net effect, due to a decrease of oestrogens and the relative increase in NKB-mediated KNDy activity, the KNDy neurons exhibit increased activity.

Increased KNDy signalling to the thermo-regulatory centre of the brain adversely affects modulation of the output to heat-dissipating mechanisms in response to input from peripheral temperature-sensing neurons. Fezolinetant blocks NKB binding on the KNDy neuron with high affinity (in vitro ki of approximately 20 nM) and selectivity compared to other members of the tachykinin family (*h*Nk+ and *h*NK2; in vitro k_i values of > 10 µM) and other G-protein coupled receptors. This binding is thought to modulate neuronal activity in the thermoregulatory centre, with the outcome of relief from VMS by "restoring" the balance between oestrogens and NKB at the neurons.

Secondary Pharmacology (Safety)

No dedicated thorough QT (TQT) study was submitted. Instead, two exposure-response analyses were conducted using ECG and PK data from two separate studies. No clinically relevant prolongation of ΔΔQTcF were predicted at clinically relevant concentrations for fezolinetant and its main metabolite ES259564, or even at up to 10-times the clinically relevant concentrations.

No signals in the non-clinical studies (hERG cell assay, telemetry study in cynomolgus monkeys and the Langendorff study) were identified that would indicate a risk for cardiovascular effects at clinically relevant concentrations of fezolinetant or its main metabolite ES259564.

In Phase II and III studies, there were no relevant cardiovascular observations. Overall, the risk of cardiovascular events induced by fezolinetant and its main metabolite therefore appears low.

6.2 Dose finding and dose recommendation

A randomised, double-blind, placebo-controlled dose-finding study investigating seven different dose groups compared to placebo was conducted. N=356 patients were included in this trial, of whom 81% completed the study. For evaluation of efficacy, four co-primary endpoints were defined, namely mean change of frequency and severity of moderate to severe VMS from baseline to week 4 and 12. As one of several secondary endpoints, responder analyses were conducted, defining response, for example, as a reduction in frequency by 70%.

Numerically, fezolinetant performed better than placebo at all doses and at both timepoints analysed. Neither for efficacy nor for overall safety was a clear trend evident for a dose-relationship.

In addition to this study, dose-finding was based on modelling and simulations, taking into consideration the fact that the mean baseline frequency of VMS in the dose-finding study had been lower than in historical studies with HRT. The models showed that, for a mean baseline consistent with historical studies, doses of 30 mg and 45 mg QD would lead to clinically meaningful reductions in the frequency of VMS.

Based on the totality of data, the 30 mg QD dosing regimen was considered the lowest effective dose, and 30 mg QD and 45 mg QD were further studied in the Phase III studies. The choice of these doses also considered the potential risk of dose-dependent elevations of transaminases (see "Safety" section below). While the 30 mg dose had been studied in the dose-finding study, the 45 mg dose, by models and simulations, was predicted to increase the probability of achieving the efficacy endpoints without an unacceptable increase in the risk for hepatotoxicity. Overall, the choice of these doses seemed acceptable.

6.3 Efficacy

To support the proposed indication, two global, randomised, double-blind, placebo-controlled pivotal studies with identical design were conducted between 2019 and 2021. In these studies, fezolinetant 30 mg and 45 mg were compared to placebo. In total, n=1022 patients were included in these studies, of whom overall approx. 80% completed the respective study.

30% of patients were recruited in Europe, the remaining patients in North America (predominantly in the US).

Patients were randomised 1:1:1 to one of the two dose groups or to placebo and treated for 12 weeks, followed by a 40-week open extension period. After week 12, patients in the active treatment arms remained on the same dose as before, while patients in the placebo arm were re-randomised to receive either 30 mg or 45 mg fezolinetant.

Inclusion criteria allowed women in the age group from 40-65 years with confirmed postmenopausal status, suffering from moderate or severe VMS, to participate in the studies. To ensure a sufficient baseline degree of symptoms, during the screening period, a minimum average of 7-8 moderate to severe VMS per day, or 50-60 per week, had to be documented in an electronic patient diary.

The inclusion and exclusion criteria allowed a broad spectrum of postmenopausal women to participate in the studies. For example, treatment-naïve patients as well as patients pretreated with HRT were included. Women with surgical menopause (i.e. a history of oophorectomy) were also eligible for inclusion. In summary, the study population can be considered representative of the target population. However, patients with pharmacologically-induced menopause were not studied, and, in particular, patients with any oestrogen-dependent malignancies were excluded from study participation.

In both pivotal studies (and, similarly, also in the dose-finding study), only ≤ 30% of screened patients were finally included in the studies. This finding suggests that frequency and severity of VMS are often overestimated by the patients.

The studies had four co-primary endpoints:

- mean change in the frequency of moderate to severe VMS from baseline to week 4
- mean change in the frequency of moderate to severe VMS from baseline to week 12
- mean change in the severity score of moderate to severe VMS from baseline to week 4
- mean change in the severity score of moderate to severe VMS from baseline to week 12

In addition, mean change in the PROMIS SD SF 8b, a questionnaire assessing the influence on sleep, from baseline to week 12 was defined as key secondary endpoint and also tested confirmatorily. In addition, the studies had numerous secondary and exploratory endpoints (including also mild VMS), like, for example, several health questionnaires (e.g. MENQOL).

In both studies, demographics and baseline characteristics were well balanced between treatment groups. In the pooled data, mean age was 54.3 years (range: 40-65 years), with slightly less than half of the patients being ≥55 years old (and 10% >60 years). 81% of patients were Caucasian, a further 17% were Black. Mean body mass index (BMI) was approx. 28 kg/m^2. 32% of patients were hysterectomised, 22% were oophorectomised. The median time interval for “time since amenorrhoea” (in HRT studies usually named as “time since menopause”) in the individual treatment groups was between 57.2 and 69.2 months, with a high variability (range 2-442 months). The same applied for the time since onset of VMS, with a median of 54.8 months and a range from 1 to 422 months. About one fifth of patients had received HRT in the past. Of those who had used HRT, 32% had stopped that treatment due to lack of efficacy.

At baseline, participants had a mean number of 11 VMS episodes per 24 hours with a mean severity score of 2.4 points.

As may be expected in this indication, a strong placebo effect was observed. Nevertheless, in both studies, both doses showed superiority over placebo in all 4 co-primary endpoints after 4 weeks as well as after 12 weeks (with a p-value of <0.001 for all comparisons in the data pool). At week 12, the frequency of moderate to severe VMS was reduced by 6-7 per day in the active treatment groups as compared to approx. 4 with placebo. Overall, the number of moderate to severe VMS was reduced by approx. 2 more events in the active groups compared to placebo, corresponding to the change defined as clinically meaningful in FDA guidance documents.

Severity was reduced by 0.58-0.66 points with active treatment as compared to 0.4 with placebo. In contrast to the convincing results for frequency of moderate to severe VMS, for severity, although statistically significant, the treatment difference between active treatment and placebo was rather small, and clinical meaningfulness may be questioned.

In addition to the primary analysis of the co-primary endpoints, several sensitivity analyses (including a tipping point analysis) were performed, providing results comparable to those of the primary analysis.

A relevant reduction in frequency was observed during the first week of treatment already. By week 4, frequency was reduced by approx. 50% in the active treatment groups, compared to 30% in the placebo arm. Results for the secondary (and exploratory) endpoints (including Patient Related Outcomes, PROs) were consistent with those for the primary analyses and supported the efficacy of fezolinetant for the treatment of menopausal VMS.

In various subgroup analyses, overall the results were consistent over all subgroups analysed, with fezolinetant showing (numerical) superiority relative to placebo regardless of the respective subgroup analysed.

Statistical comparisons between the two dose groups tested were not conducted. A numerical advantage of 45 mg over 30 mg was primarily seen in secondary and exploratory endpoints, and the overall number of significant endpoints was higher for 45 mg than for 30 mg. In particular, for the key secondary endpoint the higher dose seemed to have a stronger effect than the lower dose. For the co-primary endpoint of frequency of VMS, however, the numerical differences between the two doses tested seemed small and hardly clinically relevant. With the 45 mg dose, frequency was reduced by 19-24% more than by placebo, while for the 30 mg dose this ratio was still 14-20%.

The improvement achieved by week 12 was sustained throughout the total 52-week study period, with no evidence of reduced effect size over time suggestive of tachyphylaxis. Patients in the placebo arm showed a further reduction in the frequency and severity after being switched to active treatment, and numerical results at week 52 did not differ in a relevant way between those patients having received fezolinetant for 52 weeks and those receiving active treatment for 40 weeks only. At week 24, the numerical difference between the two dose groups was small.

6.4 Safety

For the full list of undesirable effects, see the Information for Healthcare Professional in the appendix of this report.

Fezolinetant is a first-in-class substance. Therefore, no previous experience on the safety profile is available. The Applicant undertook extensive assessments of potentially relevant safety aspects. Nevertheless, due to the limited data available so far, not all questions can be answered conclusively.

For short-term safety, the available data can be considered sufficient for characterising the safety profile of the substance. Overall, the incidence of AEs, in particular of SAEs with a possible causal relationship to fezolinetant, was relatively low. For the totality of AEs, there were no relevant differences in incidence between active treatment and placebo (incidence during the double-blind period 39-40%). The same applied to most of the individual AEs. For the vast majority of AEs, no dose-response was evident.

The most common AEs reported in patients treated with fezolinetant were headache (4.6%), upper respiratory tract infection (2.2%), blood glucose increased (1.9%), dry mouth (1.8%) and arthralgia (1.8%).

SAEs were reported in 1.5% of patients treated with 30 mg and 1.2% of those receiving 45 mg, as compared to 0.3% in the placebo group. Only 2 SAEs, both concerning an increase in liver function tests, were considered related to study treatment (as to hepatic safety, see below).

Subjective tolerability also seemed good, with a low rate of premature discontinuations of study drug due to AEs.

Long-term data, however, are available up to a treatment duration of 12 months only. During this period, compared to 12-week double-blind data, no additional safety signals were identified.

Subgroup analyses of safety data did not reveal any results of concern.

Overall, the most relevant safety aspect seems to be the potential risk of hepatotoxicity, in particular an increase in transaminases (mostly ALT). Respective findings in Phase (I and) II studies led to the application of an extensive assessment programme on hepatic safety. Liver biochemistry parameters

(ALT, AST, total bilirubin, ALP and their combination) were assessed throughout all study visits in the Phase II and Phase III programme. A (blinded) Liver Safety Monitoring Panel (LSMP) consisting of 3 independent hepatologists experienced in the assessment of drug-induced liver injury (DILI) monitored the programme and studies. Additional evaluations included assessment of time course and pattern of hepatic safety findings relative to the first dose of study drug, as well as subgroup analyses across a series of intrinsic and extrinsic factors to potentially identify population segments that may be more vulnerable to hepatic safety sequelae. Any participant who experienced criteria ALT or AST > 3 x upper limit of normal (ULN) or total bilirubin > 2 x ULN was evaluated for potential DILI by the LSMP.

The number and percentage of patients meeting predefined categories of hepatic enzyme elevations were presented by treatment group. In addition, exposure-adjusted incidence rates (defined as the number of participants with event per 100 participant-years for each category) were calculated.

ALT values >3x ULN were more frequent with active treatment than with placebo. Values >5x ULN, however, were rare, and the numbers were too low to allow any interpretation of treatment differences. For AST, changes were less common than for ALT, also preventing a meaningful comparison between active treatment and placebo.

Phase III data including the overall 52-week study period showed a clear dose response for elevations of ALT. Values >3x ULN were observed in 2.1% of patients treated with 45 mg compared to 1.3% of those receiving 30 mg only. Determination of exposure-adjusted incidence rates confirmed the assumption of a dose response.

Apart from incidences and incidence rates, information about the time to onset of liver enzyme elevations and the potential persistence of such changes was also provided. Onset of elevations in ALT, AST or bilirubin occurred at various timepoints throughout the study duration, with no overt cluster of time to onset across the treatment groups, and there was no dominant pattern of rise and fall of the transaminase values. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups.

In addition, an exposure-response analysis was conducted in a data pool of Phase II and III studies for the incidence of elevations of ALT or AST to values >3x ULN. This analysis yielded a hazard ratio of 1.471 (95% CI 1.245-1.663) for the population mean fezolinetant concentration resulting from the proposed dose of 45mg once daily.

No Hy’s law cases were identified in any of the data pools analysed.

Subgroup analyses for intrinsic and extrinsic factors did not identify a specific population with increased risk for hepatotoxicity associated with fezolinetant treatment.

In the Phase III studies, the LSMP identified 9 cases of elevated transaminases as probably related to study drug, 5 in the 45 mg group and 4 in the 30 mg group. These cases were further assessed. The final judgement of the experts was: “These events were generally hepatocellular in nature, generally occurred during the first 3 months of treatment, and typically resolved rapidly whether study drug treatment was continued or stopped.” They could not identify any patient characteristics that clearly distinguished these nine cases from the other patients in the studies. Nevertheless, they stated that the data were not able to exclude that, in a real-world setting, fezolinetant could cause more serious and/or progressive liver injuries. However, the LSMP expected such cases to be very rare.

Overall, the incidence of ALT elevations in the two doses studied in Phase III seemed acceptable. However, no risk factors for hepatotoxicity could be identified. As a consequence of these findings, monitoring of hepatic parameters is recommended in the Information for healthcare professionals.

As requested for all drugs crossing the brain barrier, a comprehensive evaluation of “CNS health” was also conducted. Overall, there was no evidence of an increase in suicidality or any other serious CNS effects.

Endometrial safety was assessed by obtaining endometrial biopsies after 12 months of treatment with fezolinetant. The results of these examinations did not give rise to any concerns. Overall, given that fezolinetant is a non-hormonal treatment that did not show any clinically relevant impact on the serum concentrations of sex hormones, an effect of endometrial health can be considered unlikely.

Dual-Energy X-ray Absorptiometry (DXA) scans showed a minimal decrease in bone mineral density (BMD) during the 12-month study period in all treatment groups, a finding not unexpected in a postmenopausal population. In the pivotal studies, in addition, bone markers were analysed. These assessments likewise yielded no relevant results.

6.5 Final clinical benefit risk assessment

Fezolinetant is the first NK3 receptor antagonist for which approval is sought. It is considered a non-hormonal treatment of menopausal VMS due to its effect on neurons in the brain involved in thermoregulation.

A statistically significant and clinically meaningful reduction in the frequency and severity of moderate to severe postmenopausal VMS versus placebo, with a rapid onset of effect, was shown in two pivotal studies. Even if only small differences in efficacy and safety were identified between the two doses, the Applicant could argue convincingly that, due to its mechanism of action (which is completely different from that of HRT), maximal receptor occupancy and sustained binding at the receptor are required for an optimal response to fezolinetant treatment. Therefore, considering all the data available, the decision of the Applicant to bring only the 45 mg dosage strength to the market seemed acceptable.

Overall, the safety profile of fezolinetant can be considered acceptable and compatible with a symptomatic treatment. Data for a treatment duration of more than one year, however, are lacking.

The most relevant safety issue seems to be the potential risk of hepatotoxicity. For the 45 mg dose, however, data seemed rather reassuring, with a low incidence and elevations of transaminases limited to ≤5x ULN in most cases.

Overall, the studies submitted support a positive benefit-risk balance of fezolinetant for the treatment of moderate to severe menopausal VMS, provided that the recommendations for monitoring of liver enzymes are followed.

However, no data are available for perimenopausal women who may also experience VMS while still menstruating, i.e. during a period when oestrogen levels are not yet completely suppressed. In particular, it is unknown whether treatment with fezolinetant might have any influence on the menstrual cycle in this population. Therefore, the indication of Veoza has been limited to postmenopausal women.

If treating breast cancer patients or other patients with pharmacologically induced menopause, prescribers should be aware that no data on efficacy and safety in such a population are available.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Veoza was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼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 new or serious adverse reactions. See the "Undesirable effects" section for advice on reporting of adverse reactions.

VEOZA™ 45 mg film-coated tablets

Composition

Active substance

Fezolinetant

Excipients

Mannitol (E421), hydroxypropyl cellulose (E463), low-substituted hydroxypropyl cellulose (E463a), microcrystalline cellulose (E460), magnesium stearate (E470b), hypromellose (E464), talcum (E553b), macrogol 8000 (E1521), titanium dioxide (E171), iron oxide red (E172).

Pharmaceutical form and active substance quantity per unit

Film-coated tablets containing 45 mg fezolinetant.
The film-coated tablets are round, light red, with debossed Astellas logo and the number ‘645’ on the same side.

Indications/Uses

Treatment of moderate to severe vasomotor symptoms (VMS) in postmenopausal patients.

Dosage/Administration

The recommended dose is 45 mg once daily.
The maximum dose is 45 mg per day.
No data are so far available for a treatment duration of more than 12 months. Consequently, the risk-benefit ratio should be verified after the first year of treatment while taking particular account of any elevations in transaminases (see “Warnings and precautions”).

Method of use
VEOZA should be taken once a day at around the same time.
The tablet should be swallowed with some fluid. The tablets may not be chewed, crushed or reduced in size in any other way. They do not have to be taken with meals.

Specific dosage recommendations

Elderly patients
No data are available for starting treatment over the age of 65 years. In this age group the use of VEOZA should only take place in well-founded cases.

Children and adolescents
The safety and efficacy of fezolinetant have not been examined in this population. VEOZA is not indicated in this age group.

Patients with impaired hepatic function
In patients with moderately or severely impaired hepatic function (Child-Pugh B or C), VEOZA is contraindicated. In patients with severe hepatic impairment (Child Pugh-C), VEOZA has not been studied (see “Pharmacokinetics”). In patients with mildly impaired hepatic function (Child-Pugh A), the use of VEOZA is not recommended (see “Warnings and precautions” and “Pharmacokinetics”).

Patients with impaired renal function
VEOZA is contraindicated for patients with severe renal impairment (eGFR less than 30 ml/min/1.73m^2) including those with end stage renal disease (see Pharmacokinetics).
No dose modification is necessary for patients 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 “Pharmacokinetics”).

Contraindications

Moderate or severe hepatic insufficiency (Child-Pugh B or C).
Severe or end stage renal impairment (eGFR < 30 ml/min/1,73 m^2).
Co-medication with CYP1A2 inhibitors (see “Interactions”).
Hypersensitivity to the active ingredient or one of the excipients depending on the “composition.”

Warnings and precautions

In case of long term treatment, the persistency of the indication should be regularly assessed.

Treatment of patients with estrogen dependent tumors
Fezolinetant has not been studied in patients with current or previous breast cancer or with other estrogen dependent tumours. This specifically applies to patients with antioestrogen therapy (which is associated with severe VMS and/or other symptoms of oestrogen deficiency). Consequently, it is not possible to make any statements about the safety of VEOZA in such

population and the decision about whether to treat these patients with fezolinetant should be based on an individual risk/benefit assessment.

Influence on liver function

In a total of three phase III studies, 2.3% of patients treated with fezolinetant (corresponding to an incidence rate of 2.7 cases per 100 women-years adjusted for the duration of exposure) experienced increases in alanine aminotransferase (ALT) and/or or aspartate aminotransferase (AST) to values >3x the upper limit of normal range (ULN). With placebo, such increases were documented in 0.9% of patients (or 1.5 cases per 100 women-years). Cases of increase intransaminase values >5x ULNwere rare. Additionally, no cases of bilirubin elevation >2x ULN were observed. The elevations of transaminase usually occurred within the first three months of treatment and were generally asymptomatic and, in most cases, reversible despite continued therapy.

Fezolinetant has not been studied in patients with severe hepatic impairment.

Liver function values (transaminases and bilirubin) should be determined before initiating therapy with fezolinetant. Monitoring should occur during the first 3 months of treatment. Further checks should be carried out at the discretion of the treating doctor depending on the individual risk constellation and if symptoms occur that could indicate liver damage (such as nausea, vomiting or jaundice). In case of symptoms suggestive of hepatic dysfunction, after assessment of alternative causes of transaminase elevations the treatment with Fezolinetant should be discontinued or temporarily interrupted in discretionary to the prescriber.

Due to the risk of transaminase elevations, a maximum dose of 45 mg per day must not be exceeded.

In a population pharmacokinetic analysis, the baseline levels of liver function values have been found to be a relevant risk factor for an increase in transaminases. Consequently, VEOZA may not be used in patients with pre-existing moderate or severe hepatic insufficiency. Use is not recommended with mildly impaired hepatic function. If such patients are treated with fezolinetant, the liver values must be closely monitored.

CYP1A2 inhibitors

In an interaction study the concomitant use of a strong CYP1A2 inhibitor fluvoxamine resulted in an increase in the AUC of fezolinetantby 9.4-fold (see “interactions”). Based on PBPK modeling, a typical moderate inhibitor, mexiletine, is likely to increase AUC by more than 3-fold. A typical weak inhibitor, cimetidine, is likely to increase AUC by approximately 2-fold. Fezolinetant must not be used together with inhibitors of CYP1A2 (see “Contraindications”).

Hormone replacement therapy (HRT)

Concomitant use of fezolinetant with a systemic or topical HRT was not investigated and the use of VEOZA in combination of a systemic HRT is therefore not recommended.

Medicinally induced menopause
Fezolinetant has been studied only in patients after natural or surgical menopause. No efficacy or safety data are available regarding the treatment of vasomotor symptoms in pharmacologically induced menopause (e.g., under treatment with GnRH-Analogues). A decision to treat these women with fezolinetant should be based on a benefit-risk consideration for the individual.

Interactions

Pharmacokinetic interactions
Fezolinetant is mainly metabolized by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19. *In vitro*, fezolinetant and its major metabolite, ES259564, are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Fezolinetant and ES259564 are not inducers of CYP1A2, CYP2B6 and CYP3A4.
The major metabolite, ES259564, is a substrate of P-glycoprotein (P-gp) but not an inhibitor of P-gp. Fezolinetant is neither a substrate nor 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.

Influence of other medicinal products on the pharmacokinetics of fezolinetant

CYP1A2 inhibitors
The concomitant use of fezolinetant with CYP1A2 inhibitors increases the Cmax and AUC of fezolinetant in the plasma.
Concomitant administration with fluvoxamine, a strong CYP1A2 inhibitor, has resulted in an increase in the Cmax of fezolinetant by 1.8-fold and the AUC by 9.4-fold. No change in the t_{max} has been observed.
Interaction studies with moderate or weak CYP1A2 inhibitors have not been conducted. Based on physiologically-based pharmacokinetic modeling, fezolinetant Cmax was predicted to increase 1.3 – 1.9-fold and AUC_{inf} 3.2 – 4.5-fold following concomitant use with mexiletine (moderate CYP1A2 inhibitor) at 200 mg or 400 mg every 8 hours.
Based on physiologically-based pharmacokinetic modeling, fezolinetant Cmax was predicted to increase 1.3 – 1.5-fold and AUC_{inf} 1.6 – 2.1-fold following concomitant use with cimetidine (weak CYP1A2 inhibitor) at 300 mg every 6 hours or 400 mg every 12 hours. The concomitant use of CYP1A2 inhibitors with fezolinetant is contraindicated.

CYP1A2 inducers
Smoking (a moderate inducer of CYP1A2) has resulted in a reduction of the Cmax of fezolinetant by 28% and the AUC by 52% compared with non-smokers. These changes in exposure were not found to be clinically relevant. A general dose modification is not recommended for smokers.

Pregnancy, lactation

Pregnancy

No data are available regarding the use of fezolinetant in pregnant women. During pregnancy, treatment with VEOZA is not indicated. Animal studies have shown reproductive toxicity at high doses (see “Preclinical data”).

Lactation

It is not known whether fezolinetant passes into human breast milk and there are no data regarding possible effects of fezolinetant on milk production or breastfed infants. In animals, fezolinetant passes into the milk. The use of VEOZA in lactating women is, therefore, not recommended.

Fertility

No data are available regarding the possible side effects of fezolinetant on human fertility.
In a fertility study in female rats, fezolinetant had no influence on fertility (see “Preclinical data”).

Effects on ability to drive and use machines

No relevant studies have been conducted.

Undesirable effects

The safety of fezolinetant has been evaluated in 2,203 postmenopausal women with VMS receiving 30 mg or 45 mg fezolinetant once daily in phase 3 clinical studies.
Across the phase 3 studies, the most common adverse reactions with fezolinetant were diarrhoea (3.2%) and insomnia (3.0%).
The most frequent adverse reactions leading to dose discontinuation with fezolinetant 45 mg were elevated alanine aminotransferase (ALT) (0.3%) and insomnia (0.2%).

Below, the adverse reactions observed with the use of fezolinetant are listed according to the MedDRA classification. Therefore, the 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).

Nervous system disorders

Common: insomnia.

Gastrointestinal disorders

Common: diarrhoea, abdominal pain.

Hepatobiliary disorders

Common: Transaminase increase.

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Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Signs and symptoms
The maximum tolerated dose has been determined to be 900 mg. At this dose, headache, nausea and paraesthesia have been observed.

Treatment
In the case of overdose, the individual should be closely monitored and supportive treatment should be considered.

Properties/Effects

ATC code
G02CX06

Mechanism of action
Fezolinetant is a nonhormonal selective neurokinin 3 (NK3) receptor antagonist which blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory centre. Fezolinetant binds to the NK3 receptor with high affinity. This affinity is higher than that of the binding to NK1 or NK2 receptors by a factor of 450. The thermoregulatory centre in the hypothalamus is innervated by KNDy neurons, which are inhibited by oestrogen and stimulated by the neuropeptide NKB. Through the menopausal transition, declining oestrogen disrupts this balance. Unopposed, NKB signalling increases KNDy neuronal activity, leading to hypertrophy of the KNDy neurons and altered activity of the thermoregulatory centre, resulting in vasomotor symptoms (VMS).

Pharmacodynamics
As a result of the administration of fezolinetant, the impaired equilibrium in the thermoregulatory centre is restored. Consequently, the number and severity of VMS are reduced.
In postmenopausal women, a transient decrease in the serum concentrations of luteinizing hormone (LH) was observed at peak fezolinetant concentration. The clinical significance of this finding is not clear. For follicle-stimulating hormone (FSH), oestradiol, testosterone and dehydroepiandrosterone sulphate, no clinically relevant changes or clear trends have been established.

Safety pharmacology

For the assessment of a possible risk of QT prolongation by fezolinetant, a model-based approach has been used. The model has not predicted any clinically relevant prolongation of the QTc interval either in therapeutic or supratherapeutic concentrations.

Clinical efficacy

SKYLIGHT 1 and SKYLIGHT 2

The efficacy of fezolinetant has been evaluated in n=1,022 postmenopausal women with moderate to severe VMS in two 12-week, randomised, placebo-controlled, double-blind phase 3 studies. Eligible for inclusion were patients aged 40-65 years who had at least 7-8 moderate to severe hot flushes per day (or at least 50-60 per week). The patients were randomised 1:1:1 to 30 mg fezolinetant, 45 mg fezolinetant or placebo. The double-blind phase was followed by a 40-week open-label extension, during which all patients were treated with fezolinetant.
The mean age of the patients included was 54 years, 80% of the patients were white, 17% were black and 1% were Asian.
The study population included both patients with natural menopause (78%) as well as those after oophorectomy (22%) and both treatment-naïve patients (79%) as well as those with previous hormone replacement therapy (HRT) (20%). 33% of the patients had a history of hysterectomy.
The studies had four co-primary endpoints in each case, namely the change compared with baseline in the frequency and severity of moderate to severe VMS after a duration of treatment of 4 or 12 weeks.
For both doses examined, statistically significant superiority compared with a placebo was shown for all four co-primary endpoints. The daily number of moderate to severe VMS had decreased by 6.4 by Week 12 with 30 mg fezolinetant and by 6.9 with 45 mg compared with a decrease of 4.4 with a placebo. Starting from a baseline score of approx. 2.4, the severity score had decreased by 0.6 by Week 12 with 30 mg and by almost 0.7 with 45 mg compared with a decrease of 0.4 with a placebo. The results for the secondary endpoints examined (including health questionnaires such as MENQoL) were consistent with regard to this.
A clinically relevant reduction in the number and severity of moderate to severe VMS had already taken place during the first week of treatment. Efficacy was maintained for the whole 52-week duration of the treatment. In patients who were changed from the placebo to fezolinetant after Week 12, the number and severity of the VMS further decreased with the active treatment and were at the end of the study similar to those in patients who had received fezolinetant over 52 weeks.

Endometrial safety

The endometrial safety of fezolinetant has been studied in a 12-month, placebo-controlled study in a total of 1,830 women, of whom n=611 were treated with 30 mg fezolinetant and n=609 were

treated with 45 mg fezolinetant. In addition, relevant data are available from a subgroup of the two pivotal studies.
The examination of endometrial biopsies after a 12-month period of treatment did not provide any indication of an increased risk of endometrial hyperplasia or malignant changes of the endometrium. In the transvaginal ultrasound, fezolinetant did not have effect on endometrial thickness compared with the placebo.

Pharmacokinetics

Absorption
After oral administration, the Cmax of fezolinetant is reached after 1 to 4 hours. The once daily administration of 20-60 mg results in dose proportional increase in the Cmax and the AUC. Steady-state was reached by Day 2, with minimal accumulation with once daily dosing. The pharmacokinetics of fezolinetant do not change with time.
Based on data from radiolabeled study, the oral bioavailability is estimated to be > 90%.

Influence of food
No clinically relevant differences in fezolinetant pharmacokinetics have been 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%). Fezolinetant is found in approximately equal proportions in red blood cells and plasma (distribution ratio of 0.9).

Metabolism
Fezolinetant is primarily metabolised by CYP1A2 in humans to yield its oxidised major metabolite ES259564. ES259564 is approximately 20-fold less active on the 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 of fezolinetant at steady state is 10.8 L/h. Following oral administration, fezolinetant is mainly eliminated in urine (77%) as the metabolite and to a lesser extent in faeces (14%). In urine, a mean of 1.1% of the administered fezolinetant dose was found as unchanged active substance and 61.7% was found as ES259564. The effective half-life ($t_{1/2}$) of fezolinetant is 9.6 hours in women with vasomotor symptoms.

Kinetics in specific patient groups

Elderly patients
The pharmacokinetics of fezolinetant have not been examined in women > 65 years.

Paediatric patients

The pharmacokinetics of fezolinetant have not been studied in subjects < 18 years.

Hepatic impairment

Single dose administration of 30 mg fezolinetant to subjects with mild hepatic impairment (Child-Pugh A), resulted in 23% higher Cmax and 56% higher AUC compared to matched controls with normal hepatic function. In women with moderate Child-Pugh Class B hepatic impairment, AUC was 96% higher compared to women with normal hepatic function, Cmax however decreased by 15%. The pharmacokinetics of fezolinetant have not been studied in patients with severe hepatic impairment (Child-Pugh C).

Mild or moderate hepatic impairment did not have a significant effect on AUC of the major metabolite, ES259564, but Cmax was decreased to 79% and 53%, respectively.

Renal impairment

Following the single-dose administration of 30 mg fezolinetant, there was no clinically relevant effect on fezolinetant exposure (Cmax and AUC) in female subjects with mild (eGFR 60 to <90 mL/min/1.73 m^2) to severe (eGFR <30 mL/min/1.73 m^2) renal impairment. The AUC of the main metabolite ES259564 was not changed in female subjects with mild renal impairment, but it increased 1.7- or 4.8-fold in moderate (eGFR 30 to <60 mL/min/1.73 m^2) and severe renal impairment. The pharmacokinetics of fezolinetant have not been studied in female patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2).

Ethnicity

The pharmacokinetics of fezolinetant does not have clinically relevant difference with regard to ethnicity.

Other factors of influence

Body weight (42 to 126 kg), age (18 to 65 years) or menopause status have not had any clinically relevant effects on the pharmacokinetics of fezolinetant.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

In female rats, the daily administration of fezolinetant for 26 weeks at doses equal to or greater than 30 mg/kg/day (safety margin: 56-fold) showed uterine atrophy and epithelial mucification of the vagina and cervix. In female cynomolgus monkeys, daily administration for 39 weeks at doses equal to or greater than 10 mg/kg/day (19-fold the human AUC_{24} at the MRHD) showed reduced ovarian activity.

Safety pharmacology

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 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 (safety margin: 60-fold). Fezolinetant inhibited the hERG channel with an IC_{50} value of 231.8 µmol/L (safety margin: 371-fold).

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

Carcinogenicity
A 2-year female rat carcinogenicity study and a 26-week carcinogenicity study in rasH2 transgenic mice revealed no evidence of drug-related carcinogenicity (safety margin: 186- and 47-fold, respectively).

Reproductive toxicity
Fezolinetant had no effect on female fertility or early embryonic development up to 100 mg/kg/day in rats (safety margin: 143-fold).

In embryo-foetal development toxicity studies, embryo-lethality in rats and rabbits was established at doses of 100 and125 mg/kg respectively (safety margin: 128- and 174-fold). The NOAEL for embryo-foetal development was 50 mg/kg/day in rats and 45 mg/kg/day in rabbits (safety margin: 62- and 16-fold, respectively).

In pre- and post-natal development study in rats, the NOAEL for maternal and foetal toxicity was 30 mg/kg/day (safety margin: 36-fold) 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 (safety margin: 204-fold) and 10 mg/kg/day for males (safety margin: 11-fold). The F_1 male showed incomplete balanopreputial separation which may delay male reproductive maturation or affect fertility.

Other information

Incompatibilities
Not applicable.

Shelf life
Do not use this medicine after the expiry date marked as "EXP" on the pack. The expiry date refers to the last day of that month.

Special precautions for storage

Do not store above 30° C. Store in the original packaging.

Keep out of the reach of children.

Authorisation number

69232 (Swissmedic)

Packs

PA/aluminium/PVC/aluminium unit dose blisters in cartons containing 30 film-coated tablets (B) and 100 film-coated tablets (B).

Marketing authorisation holder

Astellas Pharma AG, 8304 Wallisellen

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