swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lynkuet

International non-proprietary name: elinzanetant

Pharmaceutical form:	capsule, soft
Dosage strength(s):	60 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Bayer (Schweiz) AG
Marketing authorisation no.:	69917
Decision and decision date:	approved on 5 August 2025

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.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
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
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FFA	Free fatty acids
GI	Gastrointestinal
GLP	Good Laboratory Practice
HF	Hot flushes
HPLC	High-performance liquid chromatography
HRT	Hormone replacement therapy
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
KNDy	Kisspeptin / neurokinin B / dynorphin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NK	Neurokinin
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
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)
VMS	Vasomotor symptoms

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

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

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia, Canada, the UK 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

Lynkuet is used for the treatment of moderate to severe vasomotor symptoms (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 daily dose is 120 mg elinzanetant (two 60 mg capsules) once daily at bedtime.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	29 August 2024
Formal control completed	26 September 2024
List of Questions (LoQ)	24 January 2025
Response to LoQ	25 March 2025
2nd LoQ	16 May 2025
Response to 2nd LoQ	2 June 2025
Preliminary decision	30 June 2025
Response to preliminary decision	15 July 2025
Final decision	5 August 2025
Decision	approval

3 Medical context

Vasomotor symptoms (VMS, hot flushes) are a frequent symptom in women during and in the first years after menopause and are caused by decreasing oestrogen levels as ovarian function declines. Even if prevalence (60-85% of all menopausal women) is highest during the first two years after menopause, VMS may last for up to a decade (or even longer), with a “typical” duration of 7.4 years mentioned in 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 Lynkuet) 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.
Elinzanetant is a non-hormonal selective antagonist with dual specificity for the NK-1 and NK-3 receptor approved for treatment of moderate to severe menopausal VMS. It blocks binding of neurokinin B (NKB) to the KNDy neurons in the hypothalamus.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority TGA (see section 2.1 Applicant’s request / Work-sharing procedure).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to the nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority HC (see section 2.1 Applicant’s request / Work-sharing procedure).

6 Clinical aspects

6.1 Clinical pharmacology

Absorption

Elinzanetant is a small molecule (molecular weight: 668.7 Da) and is very poorly soluble in water. Solubility increases under acidic conditions. Single doses from 40 mg up to 600 mg were tested with the soft gel formulation, and doses up 160 mg were tested at steady state. The greater than dose proportional increase in exposure was approx. 20 to 50%, and was independent if taken as a single dose or at steady state. The absolute bioavailability of 52% at a dose of 120 mg appears to be driven by the first pass metabolism, as complete dissolution and uptake of elinzanetant can be assumed with the market formulation.

Food effect

The effect of food on the PK of elinzanetant was investigated with the market formulation. In the pivotal studies OASIS 1-3, the drug was administered without restrictions on food, in accordance with the intended posology of elinzanetant.

Distribution

A circadian fluctuation of the fraction unbound (f_u) of elinzanetant was observed, with a mean f_u range of 0.08% to 0.29%. The circadian fluctuation is associated with changes in free fatty acids (FFA), which modulate the binding of elinzanetant to albumin. The FFA content is dependent on food intake (i.e. FFA are decreased during the day). This finding is supported by the PopPK analysis, where a circadian change in the apparent clearance was found, depending on the f_u. The minimal clearance was found at approx. 9 am, which corresponds to the longest, overnight, fasting period, leading to high FFA content and, therefore, a low f_u.

Brain penetration of elinzanetant and its metabolites was shown by demonstrating NK-1 receptor target engagement in the prefrontal lobe using positron emission tomography (PET) imaging. A similar EC_{50} was established after a single dose and at steady state, indicating that the distribution equilibrium across the blood-brain barrier is quickly established.

Metabolism

Three principal metabolites M30/34 (stereoisomers), M27 and M18/21 (stereoisomers) were identified early in development and were quantified across multiple studies. The metabolites are formed by CYP3A metabolism and their activity to NK1 and NK3 is similar to the parent. Their exposure was well described in the target patient population.

In a human mass-balance study, elinzanetant covered 39.1% of total radioactivity in human plasma. Metabolites M30/M34, M27 and M18/M21 accounted for 13.7%, 7.6% and 4.9% of total radioactivity, respectively. All other identified metabolites covered in sum 14.3% of total radioactivity (each less than 3.5%), and approximately 80% of the total plasma radioactivity could be attributed to known structures. The unknown structures are likely attributed to other oxidative metabolites.

Elimination

Following oral administration, a median terminal elimination half-life of approximately 45 hours after multiple doses of 120 mg was estimated based on the final PopPK model. The clearance of elinzanetant from plasma is sensitive to protein binding, which leads to an increased clearance with a higher unbound fraction (f_u) based on a circadian fluctuation of f_u.
The dose instruction in the pivotal studies was evening dosing. Due to the circadian rhythm in clearance, morning dosing shows a tendency for higher exposure. The predicted magnitude of the exposure increase is in the range of 1.2 to 1.5 fold.

Special populations

Population

213 patients in the OASIS studies were Black or African American, and no effect on clearance was observed in the PopPK analysis. Dedicated PK studies were conducted in Chinese and Japanese healthy women in the target age range. At steady state, the reported exposures were not clinically relevant increased in these population.

Hepatic impairment

The effect of hepatic impairment (HI) on the PK parameters of elinzanetant and its metabolites was investigated in a clinical study in participants with mild and moderate HI. In moderate HI overall, a 2.3 fold increase in $AUC_{0\text{-}24h}$ and C_{max} was observed. Severe HI was not investigated and the effects on elinzanetant exposures are unknown. Thus, a contra-indication for patients with severe HI is warranted.

Renal impairment

The effect of renal impairment (RI) on the PK parameters of elinzanetant and its metabolites was investigated in a dedicated clinical study in participants with moderate and severe RI, even though only a very small fraction (less than 1%) is excreted unchanged through the kidneys. An increase in the unbound fraction, along with higher variability, was observed in participants with renal impairment. Thus, patients with severe RI should not be treated with elinzanetant.

Bodyweight and BMI

Bodyweight (mean and range of the OASIS 1-3 studies; 74.9 kg, 54.5–129.2 kg) and BMI (mean and range; 27.7 kg/m^2, 17.8–39.4 kg/m^2) were assessed as covariates in the PopPK model. BMI was identified as a significant covariate, where increasing BMI is associated with a reduction in the clearance of elinzanetant and the metabolite M30/34. This leads to a simulated AUC_{ss} ratio of 1.08 for elinzanetant and 1.03 for M30/34, respectively, for a population with a BMI of 34.1 kg/m^2 (90th percentile) compared to median BMI of 27.1 kg/m^2 in the OASIS studies, which is not clinically relevant.

Interactions

Effect of other therapies on elinzanetant

Based on *in vitro* data, elinzanetant is predominantly cleared by CYP3A mediated metabolism, (approx. 90%). Thus, co-administration with other strong and moderate inhibitors or strong inducers of CYP3A4 would be expected to have a significant effect on elinzanetant exposure, and this was further evaluated in clinical studies (see Information for healthcare professionals). The effects of strong and weak CYP3A inhibitors were evaluated using clinical data. The dose adaptation to 60 mg in case moderate inhibitors are used as concomitant therapies is based on PBPK modelling. This is acceptable, since it represents an interpolation.

Concomitant therapies with strong or moderate CYP3A inducers could lead to a reduction in efficacy since elinzanetant shows an exposure-dependent efficacy at the 120 mg dose level.

Effect of elinzanetant on other therapies

In vitro, elinzanetant and its principal metabolites M27, M30/34 and M18/21 are (auto)-inhibitors of CYP3A4 as well as (auto)-inducers of human CYP3A4. In a clinical DDI study, midazolam exposure was increased by 80% after 14 days of elinzanetant daily administration, confirming that the inhibitory characteristics are predominant.

Elinzanetant was identified *in vitro* as an inhibitor of the transporters BCRP, P-gp, OATP1B3, MATE1, OATP1B1 and BSEP (in order of ascending IC_{50} value). Based on clinical data, a weak BCRP inhibition can be expected, whereas the P-gp inhibition was not considered clinically relevant (see Information for healthcare professionals). No clinically relevant DDI potentials are expected for OATP1B3, MATE1, OATP1B1 and BSEP.

Pharmacodynamics

Secondary pharmacology

TQT analysis

A dedicated TQT study including a positive control (moxifloxacine) and single doses of 240 mg to 600 mg was conducted. The highest exposures were approx. 6-fold greater than the expected exposures at the therapeutic dose, and no QT prolongations were observed. The upper limit of the QTcF 90% CI at the highest observed elinzanetant plasma concentration was 3.0 ms.

Effect on driving

The effect of elinzanetant on the ability to drive was assessed in healthy female participants aged 44-65 years with doses of 120 mg and 240 mg. Zoplicone, a drug known to affect driving performance, was used as positive control.

Overall, a statistically significant trend towards poorer driving performance on the day after elinzanetant treatment initiation was observed, and the effect size appears to be in the same range as zopiclone. This effect is no longer present after multiple doses at steady state. The established thresholds for the driving performance tests corresponding to driving ability at 0.5 permille alcohol levels were not reached.

Pharmacodynamic interaction study

Alcohol interaction study

A dedicated study investigated the psychomotor and cognitive effects of elinzanetant in combination with an alcohol level of 0.6 permille. The study was conducted in male healthy volunteers at elinzanetant exposures approximately corresponding to those achieved with 120 mg soft gel capsules.

The administration of alcohol and elinzanetant was associated with decreased peak velocity and increased saccadic reaction time, reduced adaptive tracking performance, increased sleepiness (Epworth scale) and decreased alertness (Bond Lader scale), and poorer recognition scores and recognition times in the Visual Verbal Learning Test (VVLT).

Overall, the effects were small and additive compared to the effects of alcohol alone. The small effect size does not, however, warrant a dedicated warning for interactions with alcohol.

Exposure efficacy/safety relationship

The exposure-efficacy and exposure-safety relationship of elinzanetant was assessed in an ER model using the pivotal data from the OASIS 1-3 studies. The exposure parameters were calculated using sparse sampling and a population PK analysis.

Exposure-response (ER) analysis of frequency of hot flushes (HF)

Based on individual data inspection, three categories of responders were identified. The three subpopulations were ‘normal’ responder (94.6% of all participants receiving placebo), ‘worsening VMS’ (2.1%) and ‘immediate VMS relief’ (3.3%).

Significant elinzanetant treatment effects were observed on the speed of onset of effect (fast-effect) and for the overall steady-state effect, and age and disease burden at baseline were identified within model development as significant covariates. Younger patients and patients with a lower disease burden show a stronger relative reduction in the HF frequency.

Furthermore, a significant exposure-response relationship was identified. Patients with high elinzanetant exposure have a higher chance of falling within the ‘immediate VMS relief’ category (the chance is increased from 5.8% at the 5^{th} to 12.5% at the 95^{th} exposure percentile). In addition, patients within the ‘normal’ responder category show a stronger response at higher exposure levels.

The difference in the relative reduction in HF frequency was around 12% between the 5th and 95th exposure percentile compared to the overall difference to placebo, which was 23%.

The effect of bodyweight on exposure was not found to have a clinically relevant effect on the reduction in HF frequency. For concomitant treatments with moderate to strong CYP3A inducers, a less pronounced reduction in HF frequency can however be expected.

Similar treatment effects as for the frequency ER model were identified when analysing HF severity.

Exposure-safety analysis

No exposure-response relationships were observed at the investigated safety endpoints. The endpoints were increased ALT/AST and adverse events of special interest (somnolence, fatigue, and dizziness).

6.2 Dose finding and dose recommendation

Even if not explicitly called a dose-finding study, various doses of elinzanetant were studied in the so-called SWITCH-1 study. The doses chosen for this study were based on preclinical data on the one hand and the results of a proof-of-concept study on the other. From the preclinical data, it was assumed that a 95% receptor occupancy would be required to reach the maximum clinical effect, and that the respective plasma level of the active substance would have to be maintained for the complete dosing interval. Further investigations (based on modelling) had shown that this level of receptor occupancy required plasma concentrations of 19 µg/l for NK1 and 95-190 µg/l for NK3 due to the lower binding affinity (by a factor of approx. 10) of the NK3 receptor.

In the proof-of-concept study, 50 mg could clearly be ruled out to be an effective dose, while an increase from 150 mg to 300 mg was not accompanied by further improvement. As to safety, only the highest dose investigated (300 mg/day) was associated with a higher incidence of AEs, in particular somnolence.

In the SWITCH-1 double-blind dose-finding study, patients received daily doses of 40, 80, 120 or 160 mg elinzanetant or placebo for 12 weeks. Each of the doses was compared to placebo, while no formal comparison between the various doses was conducted.

Among the doses studied, 120 mg proved to be the most effective dose accompanied by acceptable safety. For the higher dose of 160 mg, no additional benefit was found. As regards efficacy, there was some evidence of a dose-response for doses between 40 mg and 120 mg. For the safety results, however, no dose-relationship was evident. However, sample size was too small to exclude such a relationship with certainty.

In addition, exposure-response modelling was performed based on data from the phase III studies. The respective models indicated that doses lower than 120 mg would be associated with decreased efficacy.

Overall, the decision to investigate (only) the 120 mg dose in the pivotal studies seems acceptable.

6.3 Efficacy

To support the proposed indication, two global, randomised, double-blind, placebo-controlled pivotal studies of almost identical design were conducted (OASIS 1 and 2). In these studies, 120 mg elinzanetant daily was compared with placebo during a 12-week double-blind study period. After week 12, all patients were treated with 120 mg elinzanetant for another 14 weeks. After the end of treatment, patients were followed up for 4 weeks. In total, n=796 patients were included in the two pivotal studies, of whom approx. 80% completed the respective study.

The studies were conducted in North America and Europe, with a sufficient proportion of European patients included overall and, in particular, in OASIS 2.

Inclusion criteria allowed women in the 40-65 age group with confirmed postmenopausal status and a BMI between 18 and 38 kg/m^2, suffering from moderate or severe VMS, to participate in the studies. To ensure a sufficient baseline degree of symptoms, a minimum of 50 moderate to severe VMS per week (corresponding to an average of 7 events per day) had to be documented in the electronic patient diary (Hot Flash Daily Diary, HFDD) during the screening period.

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 (hysterectomy and/or 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 malignancy were excluded from participation in the two pivotal studies. Patients with a history of breast cancer or at elevated risk for breast cancer are currently being studied in an additional phase III study that is still ongoing, i.e. efficacy and safety results for this population may be expected in the near future.

In addition to the efficacy parameters investigated in both studies, quality of sleep was investigated by actigraphy in a subgroup of patients in OASIS 1 only.

In both studies, only ≤ 30% of screened patients were finally included in the studies. This finding suggests that patients often overestimate the frequency and severity of VMS.

The studies had four 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, three key secondary endpoints were defined:

- A possible effect on sleep was investigated by changes in the PROMIS SD SF 8b total score from baseline to week 12.
- Mean change of frequency of moderate to severe VMS by week 1 was also defined as a key secondary endpoint.
- Assessment of quality of life was based on the change of MENQOL from baseline to week 12.

As to the question of clinical meaningfulness, a decrease by at least 2 events per day was defined as clinically relevant for VMS frequency. This definition was based on a recommendation of the FDA (2020). For severity of VMS, PROMIS and MENQOL, the question of clinical meaningfulness was based on the results of anchor-based methods using the data from OASIS 2.

In both studies, demographics and baseline characteristics were well balanced between treatment groups. In the pooled data, mean age was approx. 54.5 years. 80% of patients were White, a further 17% Black. Mean BMI was 27.8 kg/m^2. Almost one third of the patients included in the two pivotal studies had undergone hysterectomy.

The median duration of amenorrhoea differed somewhat between studies and treatment arms, being slightly longer in OASIS 1 than in OASIS 2, in particular in the placebo group. In OASIS 1, duration of amenorrhoea was 6 years in the active group as compared to 5 years in the placebo group. In OASIS 2, the median duration was 5.6 years in the active group compared to only 4.0 years in the placebo group. The range, however, was comparable between both studies, with a maximum duration of approx. 30 years.

Overall, 31.4% of patients had received prior HRT, without any relevant difference between treatment groups. Reasons for stopping HRT, however, were not documented.

At baseline, participants had a mean number of 14-15 moderate to severe VMS per day with a mean severity score of approx. 2.5 points. Baseline frequency was slightly higher in the placebo group than in the active group in both studies, while severity was completely comparable between treatment groups.

As may be expected in this indication, a strong placebo effect was observed. Nevertheless, in both studies, superiority over placebo was shown for elinzanetant at all 4 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 as well as in each of the individual studies). At week 12, the frequency of moderate to severe VMS was reduced by approx. 9 per day in the active treatment group as compared to approx. 6 with placebo. Overall, the number of moderate to severe VMS was reduced by approx. 3 more events in the active group compared to placebo. These findings are considered clinically relevant, and the treatment difference was larger than the minimal clinically relevant change defined by the FDA.

Severity was reduced by approx. 0.9 points with active treatment as compared to 0.5-0.6 points with placebo. In contrast to frequency, even if statistically significant, the treatment difference between active treatment and placebo was rather small, and clinical meaningfulness may be questioned.

Results of pre-defined sensitivity analyses were consistent with those of the primary analyses.

A relevant reduction in both frequency and severity was observed as early as the first week of treatment. By week 4, frequency was reduced by approx. 55% in the active treatment group, compared to approx. 30% in the placebo arm. Results for the secondary endpoints (including patient-reported outcomes, PROs) were consistent with those for the primary analyses and supported the efficacy of elinzanetant for the treatment of menopausal VMS.

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

The improvement achieved by week 12 was sustained throughout the total 26-week study period. Patients in the placebo arm showed a further reduction in frequency and severity after having been switched to active treatment and numerical results at week 26 did not differ in a relevant way between the patients who had received elinzanetant for 26 weeks and those who had received active treatment for 14 weeks only.

In OASIS 1, actigraphy was used in an exploratory sleep substudy. A total of 70 patients was included in this substudy, with largely comparable characteristics to those of the overall study population.

The results of the actigraphy showed a stronger improvement in mean daily sleep efficiency and mean daily wake after sleep onset with active treatment as compared to placebo. No clear trends, however, were observed for the other parameters studied (sleep duration or number and length of awakenings).

In addition to the two pivotal studies, a further randomised, double-blind, placebo-controlled Phase III study (OASIS 3) was conducted in order to generate long-term data. In this study, patients were treated with either 120 mg elinzanetant daily or placebo for 52 weeks. This makes the study the only one to provide double-blind data for more than 12 weeks.

In contrast to the pivotal study, no minimum disease severity was required, i.e. patients did not have to present with a minimum number of weekly moderate to severe VMS. Furthermore, only one primary endpoint was defined, namely the change in frequency of moderate to severe VMS from baseline to week 12. Apart from these aspects, the study design was very similar to that of the two pivotal studies.

Findings of this study supported the efficacy results of the two pivotal studies, and efficacy was maintained throughout the 52-week study period.

6.4 Safety

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

The safety profile was based on the pooled data from the OASIS 1, 2 and 3 studies as well as on the data for the 120 mg dose group in the SWITCH study. Results were consistent between all four studies included in the data pool. For short-term safety, the available data can be considered sufficient for characterising the safety profile of the substance.

Overall, elinzanetant showed a favourable safety profile and was well tolerated. Most AEs were mild or moderate. The incidence of serious adverse events was rather low, as was the incidence of early discontinuations due to AEs.

During the first 12 weeks of treatment (i.e. the period for which double-blind data are available from the pivotal studies), the overall incidence of AEs was significantly higher in patients treated with elinzanetant than in those receiving placebo (50.8% vs. 43.2%; RR 1.17 [95%-CI 1.06-1.31]). In particular, treatment-related AEs were approximately twice as common with active treatment than with placebo (22.6% vs. 10.7%; RR 2.10 [95%CI 1.65-2.69]). AEs of special interest (see below) were also significantly more common with elinzanetant than with placebo (11.0% vs. 4.5%; RR 2.44 [95%-CI 1.66-3.59]).

Study drug was discontinued permanently as a result of AEs in 7.8% of patients receiving active treatment compared to only 3.6% of those being treated with placebo (RR 2.17 [1.40-3.37]). This difference between treatment groups was primarily driven by the fact that, more patients in the active treatment group discontinued due to fatigue (1.7% of patients treated with elinzanetant compared to none receiving placebo).

The most common AEs reported during the first 12 weeks of treatment by patients receiving elinzanetant were headache (7.5%), fatigue (5.4%), somnolence (3.4%), dizziness (3.0%) and arthralgia (3.0%).

Differences in the incidence of AEs between active treatment and placebo were primarily found for AEs associated with the pharmacodynamic effects of the substance, i.e. fatigue, somnolence and dizziness.

Somnolence / fatigue were primarily reported during the first two weeks of treatment. In view of this AE, it is recommended that elinzanetant be taken in the evening at bedtime.

As the data pool only included data for the 120 mg dose, the pool does not allow any conclusion about a possible dose relationship for AEs. Overall (i.e. considering also the data for the other dose groups in the SWITCH study as well as those from the proof-of-concept study), the limited data available suggest that the most common AEs, namely symptoms such as somnolence, dizziness and fatigue, may be slightly dose-dependent, while most other AEs tended not to show any relevant dose-relationship.

The incidence of SAEs was slightly higher with active treatment than with placebo (1.2% vs. 0.9%). Only one SAE was considered possibly related to the study medication: a case of generalised tonic-clonic seizure in OASIS 2 during the open-label period in a patient who had been switched from placebo to elinzanetant after the double-blind period.

After week 12, the safety profile remained largely unchanged, and no additional safety signals were identified. However, long-term data are available for a maximum treatment duration of 12 months only.

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

As requested for all drugs that cross the blood-brain barrier, potential CNS effects and suicidality were also evaluated. Overall, there was no evidence of an increase in suicidality or any other serious CNS effects.

Endometrial safety was assessed by obtaining endometrial biopsies. The results of these examinations did not give rise to any concerns. It must be considered, however, that not all patients included in these analyses had actually received elinzanetant for 12 months. Nevertheless, an effect of elinzanetant on the endometrium seems rather unlikely.

For bone mineral density (BMD), the changes observed were within the expected range in this age group. No clinically meaningful changes were observed for bone markers either. It should be considered, however, that data are available for a treatment duration of up to 12 months only and that in a real-world setting, a much broader range of patients may be treated for a longer time. The issue of BMD will, therefore, be further followed up in the PSURs.

As serious hepatic events had been observed with another NK3 receptor antagonist, hepatic safety was investigated thoroughly in all studies. For elinzanetant, there was no evidence of any such risk. It has to be considered, however, that only a limited number of patients has been exposed in clinical

studies, so that any rare effects cannot be excluded with certainty. This issue will be further pursued during post-marketing surveillance.

Overall, the safety profile of elinzanetant can be considered acceptable and compatible with a symptomatic treatment.

6.5 Final clinical benefit risk assessment

Elinzanetant, a non-hormonal selective antagonist with dual specificity for the NK-1 and NK-3 receptor, is considered a non-hormonal treatment of menopausal VMS due to its effect on neurons in the brain that are 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.

Overall, the safety profile of elinzanetant 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 somnolence and fatigue, which were evident in particular during the first weeks of treatment. However, rare serious AEs cannot be excluded due to the limited number of patients exposed in clinical studies and, in particular, due to the limited duration of exposure for which data are available.

Overall, the studies submitted support a positive benefit-risk balance of elinzanetant for the treatment of moderate to severe menopausal VMS.

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 elinzanetant might have any influence on the menstrual cycle in this population. While no clinically relevant changes in hormone levels were identified in the phase III studies, results of a phase I study in healthy premenopausal women showed a meaningful influence on plasma concentrations of oestradiol, FSH, and LH, together with a lengthening of the cycle. Therefore, the indication of Lynkuet has been limited to postmenopausal women.

In addition, no studies with an active comparator are available, i.e. a comparison of efficacy between HRT and elinzanetant is not possible.

If treating breast cancer patients or other patients with pharmacologically induced menopause, prescribers should be aware that the study involving this population is still ongoing and no data on efficacy and safety are available so far.

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 Lynkuet 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 the reporting of adverse reactions.

Lynkuet®

Composition

Active substances

Elinzanetant.

Excipients

All-rac-alpha-tocopherol, caprylocaproyl macrogolglycerides, glycerol monocaprylocaprate, glycerol mono-oleate, polysorbate 80 (E 433).
Capsule shell: Gelatin, sorbitol 75 mg (E 420) and glycerol (E 422), red iron oxide, yellow iron oxide, titanium dioxide (E 171).
Printing ink: Ammonia solution concentrated, isopropyl alcohol, macrogol 400, polyvinyl acetate phthalate, propylene glycol (E 1520), purified water, ethanol, ethyl acetate, titanium dioxide (E 171).

Pharmaceutical form and active substance quantity per unit

Soft capsule with 60 mg elinzanetant.
Appearance
Opaque red, oblong soft capsules, with white imprint “EZN60”.

Indications/Uses

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

Dosage/Administration

The recommended daily dose is 120 mg elinzanetant (two 60 mg capsules) once daily at bedtime.
To date, no data are available for treatment durations of more than 12 months. Hence, the benefit-risk balance should be reviewed regularly after the first year of treatment.

Forgotten dose
If a dose has been forgotten, the next dose should be taken as scheduled on the following day at bedtime. Two doses should not be taken on the same day to make up for a forgotten dose.

Mode of administration
Oral use.

The capsules should be swallowed whole with water. The capsules must not be chewed, crushed or otherwise broken.
The capsules can be taken with or without food.

Special dosage instructions
Elderly patients
The safety and efficacy of elinzanetant have not been studied in women over 65 years.
In this age group, Lynkuet should only be used in justified cases.

Children and adolescents
The safety and efficacy of elinzanetant have not been studied in children and adolescents under 18 years. Lynkuet has no indication in this age group.

Patients with impaired hepatic function
No dose adjustment is required for patients with mild chronic hepatic impairment (Child-Pugh A).
Elinzanetant is not recommended for use in patients with moderate (Child-Pugh B) chronic hepatic impairment (see “Warnings and precautions”, as well as “Pharmacokinetics”, section “Kinetics in specific patient groups”).
In patients with severe hepatic impairment (Child-Pugh C), elinzanetant is contraindicated.

Patients with impaired renal function
No dose adjustment is required for patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2).
Elinzanetant is not recommended for use in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see “Pharmacokinetics”, section “Kinetics in specific patient groups”).

Co-administration with CYP3A4 inhibitors
Concomitant use of elinzanetant together with strong CYP3A4 inhibitors is contraindicated.
When moderate CYP3A4 inhibitors are used concomitantly, the recommended daily dose is 60 mg elinzanetant (one 60 mg capsule) (see “Interactions”). After discontinuation of the moderate inhibitor, Lynkuet can be used again after 3 to 5 of its half-lives at the usual dose of 120 mg once daily. This dose adjustment is based on modeling and has not been studied in clinical trials.
No dose adjustment is required when weak CYP3A4 inhibitors are used concomitantly.

Contraindications

- Severe hepatic impairment
- Concomitant use of strong CYP3A4 inhibitors (see “Warnings and precautions” and “Interactions”)

- Hypersensitivity to the active substance or any of the excipients (see “Composition”)

Warnings and precautions

Estrogen-dependent tumors
Elinzanetant has not yet been studied in patients with existing or previous breast carcinoma or other estrogen-dependent tumors. This particularly applies to patients on antiestrogen therapy (associated with severe vasomotor symptoms and/or other symptoms of estrogen deficiency).
Hence, no statements can be made regarding the safety of therapy with elinzanetant in such a population, and the decision to treat these patients with elinzanetant should be based on an individual benefit-risk assessment.

Clinically relevant interactions
Cytochrome P450 isoform 3A4 (CYP3A4) inhibitors reduce the clearance of elinzanetant, leading to greater exposure. Concomitant use of elinzanetant with strong CYP3A4 inhibitors is contraindicated. When used concomitantly with moderate CYP3A4 inhibitors, the elinzanetant dose must be adjusted (see “Dosage/Administration” and “Interactions”).
Strong or moderate CYP3A4 inducers reduce elinzanetant exposure. In the event of concomitant use of a strong or moderate CYP3A4 inducer, the patient should be informed that the efficacy of elinzanetant may be reduced. No data are available for a possible dose adjustment. Such a dose adjustment is not recommended, partly because elinzanetant exhibits non-linear absorption kinetics (see "Pharmacokinetics").

Hepatic safety
Hepatotoxicity has been reported with the use of fezolinetant, a NK-3 receptor antagonist. Clinical studies with elinzanetant have so far revealed no indications of any hepatotoxicity. However, due to the limited number of patients treated with elinzanetant in clinical studies to date, possible rare hepatic adverse reactions cannot be completely excluded.

Patients with impaired hepatic function
Use is not recommended in patients with moderate hepatic impairment. If such patients should nevertheless be treated with Lynkuet, liver function tests must be closely monitored (see “Dosage/Administration”).

Hormone replacement therapy (HRT)
Concomitant use of elinzanetant together with HRT has not been investigated. Hence, Lynkuet is not recommended for use together with systemic HRT.

Drug-induced menopause

Elinzanetant has only been studied in patients after natural or surgical menopause. There are no efficacy and safety data for the treatment of vasomotor symptoms in drug-induced menopause (e.g. under GnRH analogue treatment). The decision to treat such women with elinzanetant should be based on an individual benefit-risk assessment.

Excipients of particular interest

This medicinal product contains 75 mg sorbitol (E 420) per soft capsule. The additive effect of co-administered medicinal products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) must be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other concomitantly administered medicinal products for oral use.

Interactions

Pharmacokinetic interactions

Effect of other medicinal products on the pharmacokinetics of elinzanetant

Elinzanetant is mainly metabolized via the cytochrome P450 isoform 3A4 (CYP3A4) and is a substrate for the P-glycoprotein (P-gp) transporter protein. Hence, medicinal products that induce or inhibit CYP3A may affect the clearance of elinzanetant.

In patients taking moderate CYP3A4 inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, verapamil), the recommended daily dose of Lynkuet is 60 mg (see “Dosage/Administration” and “Warnings and precautions”).

Concomitant use of Lynkuet with grapefruit juice is not recommended.

No clinically relevant interactions with P-gp inhibitors are expected due to high permeability of elinzanetant through membranes and its main elimination through metabolism.

Table 1 shows the geometric mean ratio (GMR) of the pharmacokinetic parameters of elinzanetant when taken with/without concomitant medication with 90% confidence intervals (CI).

Table 1: Interactions between elinzanetant and other medicinal products with regard to the influence of other medicinal products on the pharmacokinetics of elinzanetant

Active substance (dosage regimen)	*Effects on drug concentration. GMR (90% CI) elinzanetant*	*Recommendation*
Itraconazole 200 mg (a strong CYP3A4 and P-gp inhibitor)	C_{max}: 3.31 (2.74-4.00) AUC: 6.32 (5.36; 7.44)	Elinzanetant must not be used together with strong CYP3A4 inhibitors (e.g.

Elinzanetant 120 mg		itraconazole, clarithromycin, ritonavir or cobicistat) (see "Contraindications"). In patients taking moderate CYP3A4 inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, verapamil), a daily dose of 60 mg elinzanetant is recommended based on predictions from physiologically-based pharmacokinetic (PBPK) models. No dose adjustment is required when weak CYP3A4 inhibitors are co-administered.
Carbamazepine 600 mg (a strong CYP3A4 and P-gp inducer) Elinzanetant 120 mg	C_{max}: 0.56 (0.50; 0.62) AUC: 0.36 (0.31; 0.41)	Strong or moderate CYP3A4 inducers may lead to a reduction in efficacy (see "Warnings and precautions").
Esomeprazole 40 mg Elinzanetant 120 mg	C_{max}: 1.01 (0.87; 1.18)	No dose adjustment is required when proton pump inhibitors are taken together with elinzanetant.

Effect of elinzanetant on the pharmacokinetics of other medicinal products

Elinzanetant is both an inhibitor and inducer of human CYP3A4 *in vitro*. In addition, elinzanetant is an inhibitor of the transporters BCRP, P-gp and OATP1B3 *in vitro*. Hence, elinzanetant may affect exposure to medicinal products eliminated primarily by CYP3A4 or the transporters BCRP, P-gp and OATP1B3. Clinical interaction studies with midazolam, a sensitive CYP3A4 substrate, showed that elinzanetant is a weak inhibitor of CYP3A4 at therapeutic doses in humans.
A slight increase in exposure was observed when elinzanetant was co-administered with rosuvastatin, a BCRP and OATP substrate.
No clinically relevant effect on exposure to dabigatran, a P-gp substrate, was observed after co-administration with elinzanetant.

Table 2 shows the geometric mean ratio (GMR) of the pharmacokinetic parameters of co-medication when taken with/without elinzanetant with 90% confidence intervals (CI).

Table 2: Interactions between elinzanetant and other medicinal products with regard to the effect of elinzanetant on other medicinal products

Active substance (dosage regimen)	*Effects on drug concentration. GMR (90% CI) elinzanetant*	*Recommendation*
Elinzanetant, multiple daily doses of 120 mg Midazolam 1 mg (a sensitive CYP3A4 substrate)	C_{max}: 1.49 (1.36; 1.64) AUC: 1.80 (1.61; 2.00)	Caution is required when elinzanetant is co-administered with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, fentanyl or tacrolimus). The information in the Information for healthcare professionals for these CYP3A4 substrates must also be observed.
Elinzanetant 120 mg Rosuvastatin 5 mg	C_{max}: 1.28 (1.11; 1.48) AUC: 1.23 (1.07; 1.40)	Elinzanetant can be used together with BCRP substrates.
Elinzanetant, multiple daily doses of 120 mg Tamoxifen, multiple daily doses of 20 mg	Tamoxifen: 1.06 (1.00; 1.13), 4-hydroxytamoxifen: 1.12 (1.06; 1.18), N-desmethyltamoxifen: 0.98 (0.93; 1.03), Endoxifen: 1.00 (0.94; 1.07)	Elinzanetant can be used together with tamoxifen.
Elinzanetant 120 mg Dabigatran 75 mg	C_{max}: 1.15 (0.75; 1.76) AUC: 1.19 (0.79; 1.81)	Elinzanetant can be used together with P-gp substrates.

Pregnancy, lactation

Pregnancy

There are no available data on the use of elinzanetant in pregnant woman. Studies in animals have shown reproductive toxicity (see “Preclinical data”).

Lynkuet has no indication during pregnancy.

Lactation

There are no human data on the possible excretion of elinzanetant or its metabolites in human milk, and it is not known whether elinzanetant might have an effect on milk production or the breastfed infant.

In animals, elinzanetant and its metabolites are excreted in milk (see “Preclinical data”). Concentrations of elinzanetant in milk were higher than in plasma. Lynkuet is not recommended for use in breast-feeding women.

Fertility

No human data are available on the possible influence of elinzanetant on fertility.

In female rats, impairment of fertility was observed at exposures markedly exceeding human exposure at the therapeutic dose (see “Preclinical data”).

Effects on ability to drive and use machines

Driving ability after administration of elinzanetant was assessed in a clinical study using computer-based driving simulation. Compared with placebo, minor impairment of driving ability was observed after the first dose, but not after multiple doses. However, the predefined, validated threshold for impaired driving ability was not exceeded.

Nevertheless, users should be advised to be careful when driving a vehicle or using machines if fatigue, lightheadedness or sleepiness occur during treatment with Lynkuet (see “Undesirable effects” and “Properties/Effects”).

Undesirable effects

The safety profile data are based on data from 4 phase II and III studies, in which a total of n=1113 postmenopausal patients with VMS received at least one dose of elinzanetant 120 mg. In these studies, the most frequently observed adverse reactions (≥ 5%) with elinzanetant were headache and fatigue.

The adverse reactions observed in clinical studies are listed below by system organ class (according to MedDRA) and frequency, with frequency categories defined as follows: very common: ≥1/10, common: ≥1/100, <1/10, uncommon: ≥1/1000, <1/100, rare: ≥1/10'000, <1/1000, very rare: <1/10’000.

Table 3: Adverse reactions observed with elinzanetant

System Organ Class (MedDRA)	Common
Nervous system disorders	Headache Sleepiness

System Organ Class (MedDRA)	Common
	Lightheadedness
Gastrointestinal disorders	Upper abdominal pain Diarrhea
Skin and subcutaneous tissue disorders	Rash (including maculopapular, papular and pruritic rash)
Musculoskeletal and connective tissue disorders	Muscle cramps/muscle tightness
General disorders	Fatigue/asthenia

Reporting suspected adverse reactions after authorization 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 ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Symptoms

In clinical studies with healthy subjects, single doses of up to 600 mg elinzanetant were investigated. The adverse reactions at higher doses were comparable with those at the therapeutic dose, but occurred slightly more frequently and with moderately higher intensity. No additional adverse reactions were observed with use of daily doses up to 240 mg for 5 days. No dose-limiting toxic effects were observed within the dose range investigated.

Therapy

There is no specific antidote.

In the event of overdose, the patient should be closely monitored. Depending on the symptoms, supportive treatment should be considered.

Properties/Effects

ATC code

G02CX07

Mechanism of action

Elinzanetant is a non-hormonal, selective neurokinin 1 (NK-1) and 3 (NK-3) receptor antagonist that blocks NK-1 and NK-3 receptor signaling on kisspeptin/neurokinin B/dynorphin (KNDy) neurons, thereby modulating neuronal activity involved in thermo- and sleep regulation. The decrease in estrogen levels during menopause is accompanied by hyperactivation of KNDy neurons in the hypothalamus, leading to altered activity of the thermo- and sleep-regulatory center. This results in so-called vasomotor symptoms (VMS).
Elinzanetant has high affinity for human NK-1 receptors (pK_i values of 8.7 to 10.2) and NK-3 receptors (pK_i values of 8.0 to 8.8), but not for human NK-2 receptors (pK_i just 6.0). Elinzanetant is more than 100-fold more selective for the human NK-3 receptor and more than 300-fold for the human NK-1 receptor than for numerous other non-NK receptors and off-targets.

Pharmacodynamics

Safety pharmacodynamics
After administration of a single oral dose of elinzanetant at doses up to 5 times the recommended dose, no clinically relevant prolongation of the QTc interval was observed.

Clinical efficacy

The efficacy of elinzanetant was investigated in two randomized, double-blind, placebo-controlled, multicenter studies (OASIS 1 and 2) in a total of n=796 postmenopausal patients. Patients aged 40-65 years experiencing at least 50 moderate-to-severe hot flashes over a period of 7 consecutive days during a screening phase were eligible for inclusion. Patients were treated with 120 mg elinzanetant or placebo in a double-blind manner for 12 weeks. All patients then received 120 mg elinzanetant for a further 14 weeks.
The mean age of enrolled patients was 54.6 years. 80.4% of the patients were white, 17.1% were black or African American and 0.5% were of Asian origin.
The study population included patients with natural menopause, as well as those post-hysterectomy (39%) or post-oophorectomy (21%). 31% of the patients had already received hormone replacement therapy (HRT).

The studies each had four primary endpoints, viz. the mean change in frequency and severity of moderate-to-severe VMS from baseline to weeks 4 and 12, taking into account both daytime and night-time VMS, with hot flashes recorded in an electronic diary. The key secondary endpoints were

the mean change in frequency of moderate-to-severe hot flashes from baseline to week 1 as per diary, the mean change in patient self-assessment (Patient-Reported Outcome, PRO) using PROMIS SD SF 8b total T-score to assess sleep disturbances and MENQOL total score to assess menopause-related quality of life from baseline to week 12.

In both studies, elinzanetant showed statistically significant superiority versus placebo across all four primary endpoints. In the pooled data from both studies, the daily number of moderate-to-severe VMS decreased with elinzanetant by 9.2 from a baseline of 14.0 by week 12. With placebo, the decrease during this period was 6.0, compared to a baseline value of 15.2. After as little as 4 weeks, a significant and clinically relevant difference was observed between elinzanetant (a decrease of 8.05 VMS per day) and placebo (a decrease of 4.9).
The baseline severity score was approximately 2.5 in both treatment groups. By week 12, it decreased by 0.9 with elinzanetant and by 0.6 with placebo. Once again, a significant difference was observed between the two groups after as little as 4 weeks. Findings for the secondary endpoints investigated (including PROMIS SD SF 8b total T-score to assess sleep disturbances and MENQOL total score to assess menopause-related quality of life) were consistent.

A clinically relevant reduction in frequency and severity of moderate-to-severe VMS was observed as early as during the first week of treatment. Efficacy was maintained throughout the entire 26-week treatment period.

In another randomized, double-blind, placebo-controlled, multicenter phase III study (OASIS 3) in n=628 postmenopausal women, the efficacy of elinzanetant was investigated over a duration of up to 12 months; efficacy of elinzanetant was maintained up to the end of treatment.

Endometrial safety
The endometrial safety of elinzanetant was investigated in the OASIS 1 and 2 studies (each lasting 6 months) and OASIS 3 (lasting 12 months) using transvaginal ultrasound and endometrial biopsies; after 12 months of treatment with elinzanetant, evaluable biopsies were available from 116 patients. Transvaginal ultrasound revealed no indications of any increase in endometrial thickness. No cases of endometrial hyperplasia or endometrial malignancies were identified in the endometrial biopsies.

Bone safety
In the OASIS 3 study, a subgroup of n=343 patients underwent DEXA scans to measure bone mineral density (BMD) at baseline and after 12 months of treatment. Mean percentage changes in BMD vs. baseline with elinzanetant were comparable to those with placebo and were within the expected age-related changes per year.

Pharmacokinetics

The steady-state exposure variables of elinzanetant in women with VMS taking 120 mg elinzanetant daily are as follows: The $AUC_{(0-24)ss}$ is 8572.0 h·µg/L with a geometric coefficient of variation (CV) of 46.7%. The peak steady-state plasma concentration ($C_{max,ss}$) is 1422.7 µg/L with a geometric CV of 34.8%.
Elinzanetant is practically insoluble in water and readily soluble under acidic conditions.

Absorption

C_{max} and AUC of elinzanetant increased disproportionately over the dose range of 40 to 160 mg once daily.
Steady-state plasma concentrations of elinzanetant were reached 5 to 7 days after daily dosing, whereupon modest accumulation (< 2-fold) was observed.
The median time to reach C_{max} of elinzanetant was 1.0 (1 to 4) hours. The absolute bioavailability of elinzanetant is 52%.
After food intake, a prolongation of T_{max} to 2.5 – 3.5 hours post-dose, as well as a reduction in C_{max} by approximately 70% and AUC by 30 – 40%, were observed. The minimum plasma concentration C_{trough} remained unchanged regardless of food intake.

Distribution

After intravenous administration, the mean steady-state volume of distribution (V_{ss}) of elinzanetant was 137 L, indicating extensive extravascular distribution. Plasma protein binding of elinzanetant is high (99.7%) and is influenced by circadian fluctuations. The blood-to-plasma ratio is between 0.6 and 0.7.
Exposure of elinzanetant in the human brain was demonstrated in clinical positron emission tomography (PET) studies.

Metabolism

Elinzanetant is primarily metabolized by CYP3A4 into three active metabolites. These metabolites have similar potency on human NK-1 and NK-3 receptors as elinzanetant.
At steady state, the geometric mean plasma AUC_{ss} for the three major metabolites corresponded to 53%, 29% and 27% of the parent compound AUC_{ss} respectively (based on the PopPK model).

Elimination

The clearance of elinzanetant after a single intravenous dose was 8.77 L/h.
After oral administration of elinzanetant, approximately 90% of the dose was excreted via feces (mainly as metabolites) and less than 1% via the urine. The half-life of elinzanetant in women with vasomotor symptoms was approximately 45 hours.

Kinetics in specific patient groups

Patients with impaired hepatic function

In patients with Child-Pugh Class A (mild) chronic hepatic impairment, a 1.2-fold increase in C_{max} and a 1.5-fold increase in $AUC_{(0-24)}$ was observed after multiple-dose administration of 120 mg elinzanetant, compared to subjects with normal hepatic function. In patients with Child-Pugh Class B (moderate) chronic hepatic impairment, mean C_{max} and $AUC_{(0-24)}$ of elinzanetant increased by 2.3-fold. Elinzanetant has not been studied in patients with Child-Pugh Class C (severe) chronic hepatic impairment.

Patients with impaired renal function

In patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), a 2.3-fold increase in $C_{max,unbound}$ and a 2.2-fold increase in $AUC_{unbound}$ were observed after administration of a single dose of 120 mg elinzanetant. In patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), a 1.9-fold increase in $C_{max,\ unbound}$ and $AUC_{unbound}$ was observed.

In patients with mild or moderate renal impairment, population pharmacokinetic analyses of clinical study data showed similar exposure (AUC) and peak plasma concentration (C_{max}) of elinzanetant as in patients with normal renal function.

Elinzanetant has not been studied in patients with end-stage renal failure (eGFR < 15 mL/min/1.73 m^2).

Age, BMI, race (white, black or African American) and ethnicity had no clinically relevant effect on the pharmacokinetics of elinzanetant.

Preclinical data

Systemic toxicity

Repeat-dose toxicity studies were conducted in rats and cynomolgus monkeys. In female rats, daily administration of elinzanetant for 4 weeks at doses of 100 mg/kg (40-fold the $AUC_{(0-24)}$ at the human therapeutic dose) showed mucification of the vaginal epithelium, uterine atrophy and persistent corpora lutea.

In a 13-week study on rats with twice-daily administration, treatment with elinzanetant at doses of ≥ 50 mg/kg/day in male and ≥ 20 mg/kg/day in female animals (4- and 7-fold, respectively, the $AUC_{(0–24\ h)}$ compared to the human therapeutic dose) resulted in tremor and muscle contractions (first observed on day 24) and convulsions (from day 34 onwards) in 10 out of 106 animals.

In the same study, daily administration of elinzanetant at doses from 100 mg/kg/day (16-fold the $AUC_{(0-24)}$ at the human therapeutic dose) showed skeletal muscle degeneration and necrosis. Convulsions were also observed in a 2-year rat study at doses from 60 mg/kg/day (20-fold the $AUC_{(0-24)}$ at the human therapeutic dose).

In cynomolgus monkeys, daily administration of elinzanetant for 39 weeks with twice-daily administration of doses from 60 mg/kg/day showed reduced cyclical ovarian activity.

Furthermore, diarrhea was observed in female animals at a dose of 80 mg/kg/day and in male animals at both 30 mg/kg/day and 80 mg/kg/day. Exposure ($AUC_{(0-24h)}$) at these doses was comparable to that at the recommended human dose.

Reproductive toxicity

In the embryofetal development studies with elinzanetant, there was no evidence of embryofetal lethality or teratogenicity at high doses up to 100 mg/kg/day in rats and up to 140 mg/kg/day in rabbits (23-fold and 1-fold the $AUC_{(0-24)}$ at the human therapeutic dose, respectively).

In the female rat fertility and early embryonic development study, there was a higher proportion of pre-implantation and post-implantation embryo losses, leading to reduced litter size and lower fetal body weights, at the dose of 100 mg/kg/day (16-fold the $AUC_{(0-24)}$ at the human therapeutic dose). These effects were not observed after doses of 25 mg/kg/day (4-fold the $AUC_{(0-24)}$ at the human therapeutic dose).

In the pre- and post-natal development studies in rats, F_0 females showed post-implantation losses, prolonged gestation length, delayed parturition and dystocia, as well as lower pup weights, at doses of 100 mg/kg/day (23-fold the $AUC_{(0-24)}$ at the human therapeutic dose). Increased total litter loss and a corresponding decrease in pup viability on postnatal day 5 was observed in the range of human therapeutic exposure.

After administration of radiolabelled elinzanetant to lactating rats, approximately 6% of the elinzanetant dose was excreted in milk.

Genotoxicity

Elinzanetant showed no genotoxic potential in a series of *in vitro* and *in vivo* genotoxicity tests including a bacterial mutation assay (Ames test), a mouse lymphoma assay and an *in vivo* bone marrow micronucleus test in rats. Additionally, the principal human metabolites of elinzanetant were negative for *in vitro* genotoxicity in the Ames test and micronucleus test.

Carcinogenicity

In a 2-year carcinogenicity study with elinzanetant in rats, an increase in uterine neoplasms and lymphomas was reported. The findings were seen at a dose from 60 mg/kg/day, representing at least 29-fold the total $AUC_{(0-24)}$ at the human therapeutic dose, and are thus not considered clinically relevant. These effects were not observed at a dose representing 7-fold the total $AUC_{(0-24)}$ at the human therapeutic dose. The increased incidence of uterine neoplasms in aged rats undergoing reproductive senescence, with pronounced reduction in body weight, resembles effects observed in

dietary restriction studies in rats and chronic, drug-induced hypoprolactinemia, a rat-specific mode of action, which is not relevant for humans.

In the 26-week carcinogenicity study with elinzanetant in transgenic mice, no drug-related neoplasms were observed up to the highest dose of 85 and 70 mg/kg/day in male and female animals, respectively (3 and 2 times the $AUC_{(0-24)}$ at the human therapeutic dose, respectively).

Safety pharmacology

Overall, non-clinical data reveal no special hazard for humans based on conventional studies of secondary pharmacodynamics, safety pharmacology and abuse potential.

In a core battery of safety pharmacology studies, elinzanetant caused no acute respiratory or neurobehavioral effects in rats at doses up to 100 mg/kg; at this dose, $C_{max, unbound}$ was at least 10-fold higher than the human C_{max} of 1423 ng/mL (= 7.1 nM free) at 120 mg/day. A cardiovascular study on monkeys showed a slight, reversible increase in heart rate (by up to 15%) and a minor reduction in body temperature (by up to 0.63°C) at single doses of 20 and 60 mg/kg; no changes were found at the low dose of 6 mg/kg. Peak drug plasma concentrations at 6 mg/kg were comparable with concentrations after the therapeutic dose of 120 mg/day in patients and, at 60 mg/kg, were up to 20-fold higher.

Elinzanetant has no proarrhythmic potential *in vitro* at concentrations of up to 1.91 micromolar (equivalent to 300 times the human therapeutic dose based on $C_{max, unbound}$) and *in vivo* (monkey) at 60 mg/kg (equivalent to 15 times the human therapeutic dose based on $C_{max, unbound}$).

Other information

Shelf life

Do not use this medicinal product after the expiry date (“EXP”) stated on the container.

Special precautions for storage

Keep out of the reach of children.
Do not store above 25°C.
Do not freeze.
Store in the original packaging.

Authorization number

69917 (Swissmedic).

Packs

Packs of 24, 60 or 180 (3 x 60) soft capsules. (B)

Marketing authorization holder

Bayer (Schweiz) AG, Zurich.

Date of revision of the text

June 2025