SUMMARY OF PRODUCT CHARACTERISTICS

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

1 NAME OF THE MEDICINAL PRODUCT

Lynkuet 60 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 60 mg of elinzanetant.

Excipient(s) with known effect

Each soft capsule contains 71 mg sorbitol (E 420), see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule (capsule).

Opaque red, oblong, soft capsule, approximately 24 mm long and 11 mm in diameter with white printing of “EZN60”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lynkuet is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 120 mg elinzanetant (two 60 mg capsules) taken orally once daily at bedtime.

Missed dose

If a dose is missed, the next dose should be taken as scheduled on the following day at bedtime.

Patients should not take two doses on the same day to make up for a missed dose.

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

Special populations

Elderly

The safety and efficacy of Lynkuet has not been established in women over 65 years of age. No dose recommendation can be made for this population.

Hepatic impairment

No clinically relevant increase in elinzanetant exposure was observed in patients with mild chronic hepatic impairment. In a clinical pharmacokinetic study, moderate chronic hepatic impairment increased the exposure of elinzanetant. Elinzanetant has not been studied in individuals with severe chronic hepatic impairment (see section 5.2).

No dose modification is required for individuals with mild (Child-Pugh A) chronic hepatic impairment.

Elinzanetant is not recommended for use in individuals with moderate (Child-Pugh B) chronic hepatic impairment (see section 5.2).

Elinzanetant is contraindicated in individuals with severe (Child-Pugh C) chronic hepatic impairment (see sections 4.3 and 5.2).

Renal impairment

Population pharmacokinetic analysis of the clinical study data indicates similar total exposure of elinzanetant in patients with mild or moderate renal impairment compared to patients with normal renal function. The available data on elinzanetant pharmacokinetics in patients with severe renal impairment is limited (see section 5.2).

The pharmacokinetics of elinzanetant has not been studied in patients with end stage renal disease (estimated Glomerular Filtration Rate [eGFR] less than 15 mL/min/1.73 m^2).

No dose modification is required for individuals with mild to moderate (eGFR 30 - 89 mL/min/1.73 m^2) renal impairment.

Elinzanetant is not recommended for use in individuals with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment (see section 5.2).

Other special populations

Co-administration with moderate CYP3A4 inhibitors

The recommended daily dose when used with moderate CYP3A4 inhibitors is 60 mg elinzanetant (one 60 mg capsule) taken orally once daily at bedtime (see section 4.5). After discontinuation of the moderate inhibitor (after 3 to 5 half-lives of the inhibitor), elinzanetant should be used at the usual dose of 120 mg once daily.

No dose adjustment is necessary based on race (see section 5.2).

Paediatric population

The safety and efficacy of elinzanetant in children and adolescents below 18 years of age has not been established. No data are available.

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

Method of administration

Lynkuet should be administered orally once daily at bedtime with or without food (see sections 4.5 and 5.2).

The capsules are to be swallowed whole with water and not cut, chewed or crushed.

4.3 Contraindications

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

Severe hepatic impairment.

Concomitant use of strong CYP3A4 inhibitors (see sections 4.4 and 4.5).

Known or suspected pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Medical examination/consultation

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

Concomitant use with other medicinal products

Cytochrome P450 isoform 3A4 (CYP3A4) inhibitors may decrease the clearance of elinzanetant, resulting in higher exposure.

Concomitant use of elinzanetant with strong CYP3A4 inhibitors is contraindicated (see sections 4.3 and 4.5). Reduce elinzanetant dosage when co-administered with moderate CYP3A4 inhibitors (see sections 4.2 and 4.5).

Concomitant use of elinzanetant with moderate to strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, St. John´s Wort) reduces elinzanetant exposure and efficacy may be reduced. Monitor elinzanetant efficacy when co-administered with moderate to strong CYP3A4 inducers (see section 4.5).

Oestrogen-dependent tumours and other types of pharmacologically induced menopause

Efficacy and safety of elinzanetant in patients with breast cancer or other oestrogen dependent tumours or patients with a history of such malignancies has not been established so far. This applies, in particular, to patients receiving anti-oestrogen treatment (which is associated with severe VMS and/or other symptoms of oestrogen deficiency). No data for other types of pharmacologically induced menopause (e.g., in those treated with GnRH analogues) are available.

The decision to use elinzanetant in such patients should be based on individual benefit-risk considerations.

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

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

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

Drug-induced liver injury (DILI)

Elevations in serum alanine aminotransferase (ALT) levels and serum aspartate aminotransferase (AST) at least 3 times the upper limit of normal (ULN) were observed in women treated with products from a similar class. Liver function testing is recommended before starting treatment with elinzanetant.

Liver function testing should be performed if symptoms suggestive of liver injury occur.

Information about excipients

This medicinal product contains 71 mg sorbitol in each capsule.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on elinzanetant

Elinzanetant is metabolised via CYP3A4 and is a substrate for the P-glycoprotein (P-gp) transporter protein.

CYP3A4 and P-gp inducers (substances increasing the clearance of elinzanetant)

Co-administration of multiple daily doses of carbamazepine (600 mg), a strong CYP3A4 and P-gp inducer, and elinzanetant 120 mg resulted in a decrease of C_{max} by 44% and AUC by 64% of elinzanetant.

CYP3A4 and P-gp inhibitors (substances decreasing the clearance of elinzanetant)

Co-administration of multiple daily doses of itraconazole (200 mg), a strong CYP3A4 and P-gp inhibitor, and elinzanetant 120 mg resulted in an increase of approximately 3.3-fold in C_{max} and between 4.6-fold and 6.3-fold in AUC of elinzanetant.

Physiologically Based Pharmacokinetic (PBPK) modelling predictions after co-administration of 120 mg elinzanetant with the moderate CYP3A4 inhibitor erythromycin showed a 3.0-fold increase of AUC and 2.0-fold increase for C_{max} of elinzanetant. PBPK predictions after co-administration of 60 mg elinzanetant with the moderate CYP3A4 inhibitor erythromycin showed a 1.4-fold increase of AUC and no increase for C_{max} compared to 120 mg elinzanetant alone. PBPK predictions after co-administration of 120 mg elinzanetant with the weak CYP3A4 inhibitor cimetidine showed a 1.5-fold increase of AUC and 1.3-fold increase for C_{max} of elinzanetant.

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

Elinzanetant should not be used together with strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir or cobicistat) (see sections 4.3 and 4.4).

In patients taking moderate CYP3A4 inhibitors (e.g., erythromycin, ciprofloxacin, fluconazole, verapamil) the recommended daily dose of elinzanetant is 60 mg.

The concomitant use of elinzanetant with grapefruit juice is not recommended.

Effects of elinzanetant on other medicinal products

Elinzanetant is a weak inhibitor of CYP3A4. Co-administration of midazolam, a sensitive substrate of CYP3A4, and multiple daily doses of elinzanetant 120 mg resulted in an increase of 1.5-fold in C_{max} and 1.8-fold in AUC of midazolam.

Caution is required when co-administering Lynkuet with sensitive CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, fentanyl and tacrolimus). The related recommendation in the product information of these CYP3A4 substrates should be followed.

Co-administration of multiple daily doses of tamoxifen 20 mg and elinzanetant 120 mg resulted in no clinically relevant changes in the pharmacokinetics of tamoxifen and its metabolites, N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of elinzanetant in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy should be prevented in women of child-bearing potential by using effective contraception during treatment with Lynkuet. If pregnancy occurs during use of Lynkuet, treatment should be withdrawn.

Breast-feeding

There are no data on the presence of elinzanetant or its metabolites in human milk.

Excretion of elinzanetant and its metabolites in milk has been demonstrated in rats (see section 5.3). Use of Lynkuet in lactating women is not recommended.

Fertility

No human data on the effect of elinzanetant on fertility are available.

In female rats an impairment of fertility was observed at exposures markedly exceeding the exposure of humans at the therapeutic dose (see section 5.3).

4.7 Effects on ability to drive and use machines

Elinzanetant may cause undesirable effects like fatigue, dizziness or somnolence (see section 4.8). Women should be advised to be careful when driving or using machines if such symptoms occur during treatment with Lynkuet (see section 5.1).

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions (≥5%) with elinzanetant 120 mg during clinical studies were headache (7.8%) and fatigue (5%).

Tabulated list of adverse reactions

The following information is based on data from 1113 treated postmenopausal women with VMS, who received at least one dose of elinzanetant 120 mg, in phase III (OASIS 1, OASIS 2, OASIS 3) or phase II (SWITCH-1) clinical studies.

The adverse reactions observed during clinical studies in women treated with elinzanetant are listed in Table 1.

These are classified according to the MedDRA System Organ Class (SOC).

Adverse reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: 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); not known (cannot be estimated from the available data).

Table 1: Adverse reactions observed with elinzanetant

System Organ Class (MedDRA)	Common
Nervous system disorders	Dizziness Headache [a] Somnolence [b]
Gastrointestinal disorders	Abdominal pain [c] Diarrhoea [d]
Skin and subcutaneous tissue disorders	Rash [e]
Musculoskeletal and connective tissue disorders	Muscle spasms [f]
General disorders and administration site conditions	Fatigue [g]

[a] Including sinus headache, tension headache

[b] Including hypersomnia

[c] Including abdominal discomfort, abdominal pain lower/upper, gastrointestinal pain

[d] Including frequent bowel movements, intestinal transit time decreased

[e] Including rash maculo-papular, rash popular, rash pruritic

[f] Including muscle tension, musculoskeletal stiffness

[g] Including asthenia

Seizures or other convulsive disorders

A total of 7 patients with a history of seizures were included in the clinical trials. One of these patients reported generalized tonic-clonic seizure 46 days after initiating treatment with Lynkuet. The patient had not experienced seizures or required anti-seizure medications for at least eight years prior to starting Lynkuet. A causal relationship between Lynkuet and a risk for seizures has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There were no cases of overdose reported in clinical studies.

Single doses of elinzanetant up to 600 mg have been tested in clinical studies in healthy volunteers. Adverse reactions at higher doses were similar to those observed with the therapeutic dose, but occurred slightly more often and with moderately higher intensity. Multiple once daily doses up to 240 mg over 5 days were well tolerated. No dose limiting toxicities were observed with tested doses.

In the case of overdose, the individual should be closely monitored, and supportive treatment should be considered based on signs and symptoms.

There is no specific antidote for Lynkuet.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other gynaecologicals, other gynaecologicals, ATC code: G02CX07

Mechanism of action

Elinzanetant is a non-hormonal, selective neurokinin 1 (NK_1) and 3 (NK_3) receptors antagonist. It blocks NK_1 and NK_3 receptor signalling on kisspeptin/neurokinin B/dynorphin (KNDy) neurons to modulate neuronal activity involved in thermo- and sleep regulation. KNDy neurons in the hypothalamus are hyperactivated due to oestrogen decline in menopause.

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 (as

shown by a low pK_i of 6.0). Elinzanetant is more than 100-fold selective for the human NK_3 receptor and more than 300-fold for the human NK_1 receptor versus multiple other non-NK receptors and off-targets.

Pharmacodynamic effects

No clinically relevant prolongation of the QTc interval was observed after single oral administration of elinzanetant at doses up to five times the maximum recommended dose.

Clinical efficacy and safety

The efficacy and safety of elinzanetant were investigated in two similar randomised, double-blind, placebo-controlled, multicentre phase III studies (OASIS 1 and 2). A total of 796 postmenopausal women were randomised 1:1 to receive elinzanetant 120 mg or placebo once daily at bedtime for 12 weeks, followed by elinzanetant for 14 weeks, for a total treatment of up to 26 weeks. Women who had at least 50 moderate to severe hot flushes (HF), including nighttime HF, per week were enrolled in OASIS 1 and 2.

In OASIS 1 and 2 studies, the following patient demographics were balanced between treatment groups. The mean age of women was 54.6 years (range 40-65). Most women were White (80.4%), 17.1% were Black or African American, 0.5% Asian, and 8.5% with Hispanic or Latino ethnicity. The study population also included women with prior hysterectomy (38.8%), prior uni-/bilateral oophorectomy (20.6%), or prior Hormone Replacement Therapy (HRT) use (31.4%).

The primary efficacy endpoints in OASIS 1 and 2 were the mean change in frequency of moderate to severe HF from baseline to weeks 4 and 12, including day and night HF, measured using a Hot Flush Daily Diary (HFDD). The key secondary endpoints were the mean change in severity of moderate to severe HF from baseline to weeks 4 and 12, and the mean change in frequency of moderate to severe HF from baseline to week 1 using HFDD, the mean change in the Patient-Reported Outcome (PRO) instruments Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) to assess sleep disturbances total T-score, and Menopause-specific Quality of Life (MENQOL) total score to evaluate menopause-related quality of life from baseline to week 12.

In OASIS 1 and 2 elinzanetant treatment groups showed statistically significant and clinically meaningful reduction in frequency of moderate to severe HF from baseline to weeks 4 and 12 compared to placebo.

In OASIS 1 and 2 elinzanetant treatment groups showed a statistically significant reduction in severity of moderate to severe HF from baseline to weeks 4 and 12 compared to placebo.

Results of the change in mean frequency and severity of moderate to severe HF over 24 hours from OASIS 1 and 2 are shown in Table 2.

Table 2: Mean change in frequency and severity of moderate to severe HF from baseline to Weeks 4 and 12 (OASIS 1 and 2)

	OASIS 1			OASIS 2		
Parameter	**Elinzanetant 120 mg (N=199)**	**Placebo (N=197)**	**Difference elinzanetant – placebo 95% CI p-value** [a]	**Elinzanetant 120 mg (N=200)**	**Placebo (N=200)**	**Difference elinzanetant – placebo 95% CI p-value** [a]
Frequency at **baseline** Mean (SD)	13.38 (6.57)	14.26 (13.94)		14.66 (11.08)	16.16 (11.15)	
Change from baseline to week 4 LS-Means (SE)	-7.60 (0.43)	-4.31 (0.43)	-3.29 (0.61) -4.47, -2.10 <0.0001	-8.58 (0.49)	-5.54 (0.49)	-3.04 (0.69) -4.40, -1.68 <0.0001
Change from baseline to week 12 LS-Means (SE)	-8.66 (0.58)	-5.44 (0.59)	-3.22 (0.81) -4.81, -1.63 <0.0001	-9.72 (0.50)	-6.48 (0.49)	-3.24 (0.69) -4.60, -1.88 <0.0001
Severity at **baseline** Mean (SD)	2.56 (0.22)	2.53 (0.23)		2.53 (0.24)	2.54 (0.24)	
Change from baseline to week 4 LS-Means (SE)	-0.73 (0.04)	-0.40 (0.04)	-0.33 (0.06) -0.44, -0.23 <0.0001	-0.75 (0.04)	-0.53 (0.04)	-0.22 (0.06) -0.34, -0.09 0.0003
Change from baseline to week 12 LS-Means (SE)	-0.92 (0.05)	-0.52 (0.05)	-0.40 (0.07) -0.54, -0.25 <0.0001	-0.91 (0.06)	-0.62 (0.05)	-0.29 (0.08) -0.44, -0.14 <0.0001

CI = Confidence Interval, LS-Means = Least Squares Means, SD = Standard Deviation, SE = Standard Error

[a] one-sided p-value

[b] key secondary endpoint

The results in reduction of frequency and severity of moderate to severe HF were consistent across various patient subgroups such as race, ethnicity, BMI and smoking status.

For the key secondary endpoints assessed in the OASIS 1 and 2 trials, women treated with elinzanetant vs placebo showed statistically significant improvement in sleep disturbances from baseline to week 12 as assessed by the PROMIS SD SF 8b total T score (difference in LS Means (SE) for OASIS 1: -5.58 (0.82) [95% CI, -7.18 to -3.98], P < 0.0001; OASIS 2: -4.32 (0.74) [95% CI, -5.77 to -2.86], P < 0.0001). Women treated with elinzanetant showed statistically significant improvement in the menopause related quality of life vs placebo from baseline to week 12 as assessed by the MENQOL total score (difference in LS means (SE) for OASIS 1: -0.42 (0.11) [95% CI, -0.64 to -0.20], P < 0.0001; OASIS 2: -0.30 (0.12) [95% CI, -0.53 to -0.07], P = 0.0059). A statistically significant reduction in frequency of moderate to severe HF was observed with elinzanetant vs placebo from baseline to week 1 (difference in LS Means (SE) for OASIS 1: -2.45 (0.46) [95% CI, -3.36 to -1.55], P < 0.0001; OASIS 2: -1.66 (0.55) [95% CI, -2.73 to -0.58], P = 0.0013).

The OASIS 3 study was a randomised, double-blind, placebo-controlled, multi-centre phase III study with a primary efficacy endpoint of mean change in frequency of moderate to severe HF from baseline to week 12 and a long-term safety evaluation up to 52 weeks in 628 postmenopausal women (randomised 1:1 to elinzanetant or placebo). Elinzanetant showed a statistically significant outcome on the primary endpoint with a stable effect as evaluated up to week 50.

Endometrial safety

The endometrial safety of elinzanetant was assessed in the clinical studies OASIS 1, 2 (6 months duration) and OASIS 3 (12 months duration) by transvaginal ultrasound and endometrial biopsies. The 12 month placebo-controlled study investigated a total of 628 women of whom 313 women received elinzanetant. Transvaginal ultrasound testing showed no increase in endometrial thickness. There were no cases of endometrial hyperplasia or malignancy identified in the endometrial biopsies.

Bone safety

Bone safety of elinzanetant was assessed in 343/628 women in the OASIS 3 study by bone mineral density (BMD) measurements. After 52 weeks of treatment, the observed mean percentage changes from baseline in BMD with elinzanetant was comparable to that with placebo and was within the expected age-related changes per year.

Driving ability

Driving performance was assessed at 9 hours after bedtime administration of elinzanetant 120 mg and 240 mg (two times the recommended dose) in a randomised, double-blind, placebo- and active-controlled, four-period crossover study in 64 healthy women (mean age 52.1 years) using a computer-based driving simulation. The primary outcome measure was the difference from placebo in the Standard Deviation of Lateral Position (SDLP). Driving performance was evaluated using a validated threshold established in a population with blood alcohol concentration of 0.05%. The mean SDLP did not reach the threshold for driving impairment after

administration of elinzanetant 120 or 240 mg. Compared to placebo minor differences in mean SDLP, not exceeding the predefined threshold for driving impairment, were seen with both doses after one day but not after five consecutive days of elinzanetant administration.

5.2 Pharmacokinetic properties

Elinzanetant C_{max} and AUC increased in greater than dose-proportional manner (20% - 50%) over the dose range from 40 mg - 160 mg once daily (0.33 - 1.33 times the recommended dose).

Steady state plasma concentrations of elinzanetant were reached 5 – 7 days after daily dosing, with modest (<2-fold) accumulation.

Elinzanetant is practically insoluble in water and slightly soluble under acidic conditions.

Absorption

The median (range) time to reach elinzanetant C_{max} was 1.0 (1 - 4) hours. The absolute bioavailability of elinzanetant is 52%.

The minimum effective steady state plasma concentrations (C_{trough}) to ensure almost complete receptor-occupancy were unchanged with or without food intake.

Distribution

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

Biotransformation

Elinzanetant is primarily metabolised by CYP3A4 to yield three active metabolites. These metabolites have similar potency for the human NK_1 and NK_3 receptors as compared to elinzanetant. The ratio of these metabolites to parent in plasma is approximately 0.39.

Elimination

The clearance of elinzanetant after single intravenous dose was 8.77 L/h.

Following oral administration of elinzanetant, approximately 90% of the dose was excreted with faeces (mainly as metabolites) and less than 1% with urine. The half-life of elinzanetant was approximately 45 hours in women with VMS.

Special populations

Hepatic impairment

Following multiple-dose administration of 120 mg elinzanetant in patients with Child-Pugh Class A (mild) chronic hepatic impairment, mean elinzanetant C_{max} increased by 1.2-fold and $AUC_{(0-24)}$ increased by 1.5-fold, relative to subjects with normal hepatic function. In patients with Child-Pugh Class B (moderate) chronic hepatic impairment, mean elinzanetant C_{max} and $AUC_{(0-24)}$ increased by 2.3-fold.

Elinzanetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment.

Renal impairment

In a clinical pharmacokinetic study, following single-dose administration of 120 mg elinzanetant in patients with moderate (eGFR 30 - 59 mL/min/1.73 m^2) renal impairment, mean elinzanetant $C_{max, unbound}$ increased by 2.3-fold and $AUC_{unbound}$ increased by 2.2-fold. In patients with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment, mean elinzanetant $C_{max, unbound}$ and $AUC_{unbound}$ increased by 1.9-fold.

Population pharmacokinetic analysis of the clinical study data indicates similar total exposure of elinzanetant in patients with mild and moderate renal impairment compared to patients with normal renal function.

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

Paediatric population

The safety and efficacy of elinzanetant has not been studied in children and adolescents below 18 years of age.

Other special populations

No clinically relevant differences in effects of race on the pharmacokinetics of elinzanetant were observed (see section 5.1).

5.3 Preclinical safety data

Systemic toxicity

Repeat dose toxicity studies were conducted in rats and cynomolgus monkeys.

Mortality or sacrifice in moribund condition occurred at oral doses ≥ 20 mg/kg/day for 13 weeks in rats (greater than 7-fold human exposure based on $AUC_{(0-24)}$) after preceding occurrence of tremor, muscle contractions and later also convulsions and ≥ 60 mg/kg/day for 4 weeks in cynomolgus monkeys (greater than 3.6-fold human exposure based on $AUC_{(0-24)}$) due to severe diarrhoea.

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 single 13-week study in rats with twice daily dosing, daily administration of elinzanetant at doses equal to 50 or 20 mg/kg/day in males or females (4- or 7-fold the $AUC_{(0-24)}$ at the human therapeutic dose) led to involuntary muscle contractions from day 24 in 10/88 animals, which later also had convulsions from day 34. In the same study, daily administration of elinzanetant at doses equal to or greater than 100 mg/kg (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 equal to or greater than 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 dosing at doses equal to or greater than 60 mg/kg/day showed reduced cyclical ovarian activity. In the same study, diarrhoea was observed at doses of 30 and 80 mg/kg/day in males, but not at 60 mg/kg/day, and at 80 mg/kg/day in females. Plasma exposures ($AUC_{(0-24)}$) at these doses were similar to those in humans at the recommended clinical dose in females.

<u>Embryotoxicity/Teratogenicity/Reproduction toxicity</u>

In the embryo-foetal developmental studies with elinzanetant no evidence of embryo-foetal lethality or teratogenicity occurred 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, increased percentages of pre-implantation and post-implantation embryo loss, resulting in reduced litter size, and lower foetal body weights were seen at the dose of 100 mg/kg/day (16-fold the $AUC_{(0-24)}$ at the human therapeutic dose). These effects were not observed following dosing at 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 loss, increase in 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). Increase in total litter loss and corresponding decrease of pup viability on post-natal day 5 were observed in the range of human therapeutic exposure.

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

Phototoxicity

Elinzanetant binds to melanin and absorbs light in the visible part of the spectrum. Phototoxicity was seen *in vitro* at a concentration of 316 ng/mL, yielding 67-times the C_{max} at the human therapeutic dose. No phototoxicity was seen at the next lowest concentration (100 ng/mL; 21-times the unbound clinical C_{max} at the clinical dose of 120 mg/day). Clinical relevance is unknown but cannot be excluded.

Genotoxicity

Elinzanetant showed no genotoxic potential in a panel 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 genotoxicity *in vitro* in the Ames and micronucleus tests.

Carcinogenicity

The carcinogenic potential of elinzanetant was investigated in a 6-month study in transgenic (Tg.rasH2) mice and in a 2-year study in female rats, both conducted by the oral route. Elinzanetant was not carcinogenic in transgenic mice up to the highest dose level tested (85 mg/kg/day in males and 70 mg/kg/day in females), yielding exposure to elinzanetant [plasma AUC] 3- and 2-times higher in the respective sexes than in patients at the recommended clinical dose of 120 mg/day.

A treatment-related increase in uterine neoplasms (endometrial adenocarcinoma and squamous cell carcinoma) and malignant lymphoma was observed with elinzanetant in rats. The findings were seen at a dose equal to or greater than 60 mg/kg/day representing at least 29-fold the total AUC at the human therapeutic dose, and are thus not considered to indicate that elinzanetant poses a particular carcinogenic risk to patients. These effects were not observed at a dose representing 7-fold the total AUC at the human therapeutic dose. The increased incidence of uterine neoplasms in aged rats undergoing reproductive senescence with pronounced body weight reduction resembles effects observed in dietary restriction studies in rats and chronic, drug-induced hypoprolactinaemia, a rat-specific mode of action, which is not relevant for humans.

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 did not produce acute respiratory or neurobehavioral effects in rats at doses up to 100 mg/kg. At this dose, the respective $C_{max, unbound}$ was at least 28-fold higher compared to the human exposure at 120 mg/day. There was a slight and reversible increase (up to 15%) in heart rate and a minor reduction in body temperature (up to 0.63 °C) in a monkey cardiovascular study at single doses of 20 and 60 mg/kg, without changes at the low dose of 6 mg/kg. Maximal unbound drug plasma concentrations at 6 mg/kg were similar to those following the therapeutic dose of 120 mg/day in patients, and up to 15-fold higher at 60 mg/kg.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling

All-rac-α-tocopherol

Caprylocaproyl macrogolglycerides

Glycerol monocaprylocaprylate

Glycerol mono-oleate

Polysorbate 80

Capsule shell

Gelatine

Sorbitol special-glycerine (E 420)

Iron oxide red

Iron oxide yellow

Titanium dioxide

Printing ink

Macrogol 400

Polyvinyl acetate phthalate

Propylene glycol

Titanium dioxide

Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium/PET/paper blister containing 12 soft capsules.

Each pack contains 24, 60 or 180 soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0759

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/07/2025

10 DATE OF REVISION OF THE TEXT

08/07/2025