ANNEX I

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 elinzanetant.

Excipient with known effect

Each soft capsule contains 71 mg sorbitol (E 420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule (capsule)

Opaque red, oblong, 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 section 5.1)
- caused by adjuvant endocrine therapy (AET) related to breast cancer (see section 5.1).

4.2 Posology and method of administration

Posology

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

Benefits of symptomatic treatment should be periodically assessed (e.g. during routine and/or cancer follow-up care) as the need for treatment can vary by individual or change over time.

Co-administration with moderate CYP3A4 inhibitors
The recommended daily dose when used with moderate CYP3A4 inhibitors is 60 mg (one 60 mg capsule) elinzanetant 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.

Missed dose
If a dose is missed, the next dose should be taken as scheduled on the following day.
Patients should not take 2 doses on the same day to make up for a missed dose.

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

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

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

Renal impairment
For patients with moderate to severe (eGFR less than 60 mL/min/1.73 m^2) renal impairment the recommended daily dose is 60 mg (one 60 mg capsule) elinzanetant at bedtime (see section 5.2).

No dose modification is required for patients with mild (eGFR 60 - 89 mL/min/1.73 m^2) renal impairment.

Paediatric population
There is no relevant use of elinzanetant in the paediatric population in the indications moderate to severe VMS associated with menopause or caused by AET.

Method of administration

Lynkuet is for oral use.

The capsules should be taken orally once daily at bedtime.
The capsules should be swallowed whole with water. The capsules should not be cut, chewed or crushed as they contain an oily solution.

The capsules can be taken with or without food (see section 5.2) but should not be taken with grapefruit or grapefruit juice (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known or suspected pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Concomitant use with other medicinal products

Cytochrome P450 isoform 3A4 (CYP3A4) inhibitors may decrease the clearance of elinzanetant, resulting in higher exposure. The concomitant use of elinzanetant with strong CYP3A4 inhibitors is not recommended. For concomitant use with moderate CYP3A4 inhibitors reduce the dose of elinzanetant (see section 4.5).

Elinzanetant in combination with other breast cancer treatments

The use of elinzanetant has been evaluated in combination with AET consisting of aromatase inhibitors or tamoxifen, with or without GnRH agonists. A decision to treat women with elinzanetant who receive medication other than those evaluated in the clinical studies should be based on an individual benefit-risk consideration.

Concomitant use of hormone replacement therapy (HRT) with oestrogens to treat VMS associated with menopause

Concomitant use of elinzanetant and HRT with oestrogens has not been studied, and therefore concomitant use is not recommended. Local vaginal preparations can be used.

Excipient with known effect

Sorbitol
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 when 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 inhibitors (substances increasing exposure to 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 area under the curve (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-fold increase of AUC and 2-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 in 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.

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

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

If used concomitantly with moderate CYP3A4 inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, verapamil) the daily dose of elinzanetant is 60 mg (see section 4.2).

No dose adjustment is required for weak CYP3A4 inhibitors.

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 elinzanetant with sensitive CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, fentanyl or tacrolimus). The related recommendation in the product information of these CYP3A4 substrates should be followed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lynkuet is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during treatment with Lynkuet, the treatment should be withdrawn.
There are no or limited data from the use of elinzanetant in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).Women of child-bearing potential have to use effective contraception during treatment. Non-hormonal contraceptives are recommended for this population.

Breast-feeding

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

Fertility

No human data on the effect of elinzanetant on fertility are available. In the fertility study in female rats, elinzanetant did not affect fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Elinzanetant has minor influence on the ability to drive and use machines. Somnolence and fatigue are potential adverse reactions to elinzanetant. Therefore, women should be advised to be careful when driving or using machines if they experience such reactions during treatment with elinzanetant (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions (≥5%) with elinzanetant are:
- for VMS associated with menopause: headache (7.8%) and fatigue (5.0%)
- for VMS caused by AET: fatigue (14.2%), somnolence (9.5%), diarrhoea (7.1%), depression (6.2%), and muscle spasm (5.2%).

Tabulated list of adverse reactions

The safety profile of elinzanetant is based on data from women who received at least 1 dose of 120 mg elinzanetant:
- 1 113 treated women with VMS associated with menopause in 3 phase III (OASIS 1, OASIS 2, OASIS 3) and 1 phase II (SWITCH-1) clinical studies and
- 465 treated women with VMS caused by AET in a separate phase III clinical study (OASIS 4).

The adverse reactions are listed in table 1. They are classified according to MedDRA System Organ Class. 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 available data).

Table 1: Adverse reactions

System organ class	Frequency	VMS associated with menopause	VMS caused by AET
Psychiatric disorders	Common		Depression Depressive mood
Nervous system disorders	Common	Dizziness Headache Somnolence	Dizziness Somnolence Vertigo
Gastrointestinal disorders	Common	Abdominal pain Diarrhoea	Diarrhoea
Hepatobiliary disorders	Common		Alanine aminotransferase (ALT) increased*
	Uncommon	Alanine aminotransferase (ALT) increased* Aspartate aminotransferase (AST) increased*	Aspartate aminotransferase (AST) increased*
Skin and subcutaneous tissue disorders	Common	Rash	Alopecia
	Uncommon	Photosensitivity reactions*	Photosensitivity reactions*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms	Muscle spasms
General disorders and administration site conditions	Very common		Fatigue
	Common	Fatigue	

* see 'description of selected adverse reactions'

Description of selected adverse reactions

Photosensitivity reactions
In the pooled safety data up to 52 weeks, photosensitivity reactions were reported in 0.4% of patients treated with elinzanetant and in 0.1% of patients treated with placebo.
In OASIS 4 up to 52 weeks, photosensitivity reactions were reported in 0.9% of patients treated with elinzanetant and in 0.6% of patients treated with placebo.

ALT and AST increased
In the pooled safety data up to 52 weeks, the term ALT increased was reported in 0.6% of patients treated with elinzanetant and in 0.5% of patients treated with placebo. The term AST increased was reported in 0.4% of patients treated with elinzanetant and in 0.5% of patients treated with placebo.
In OASIS 4 up to 52 weeks, the term ALT increased was reported in 1.1% of patients treated with elinzanetant and in 0.6% of patients treated with placebo. The term AST increased was reported in 0.6% of patients treated with elinzanetant and in none of the patients treated with placebo.

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

4.9 Overdose

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. Safety and tolerability of multiple once daily doses up to 240 mg over 5 days were similar compared to the recommended daily dose of 120 mg elinzanetant.

In the case of overdose, the patient 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 receptors signalling on kisspeptin/neurokinin B/dynorphin (KNDy) neurons, which is postulated to normalise neuronal activity involved in thermo- and sleep regulation.

Pharmacodynamic effects

No clinically relevant prolongation of the QTc interval was observed after single oral administration of elinzanetant at doses up to 5 times the maximum recommended dose.

In healthy premenopausal women having received elinzanetant over 21 days, results showed changes of plasma concentrations of sexual hormones (i.e. dose-related reductions of LH, oestradiol, and progesterone) and prolongation of the menstrual cycle. Changes in female sex hormones that were observed, are consistent with the anticipated pharmacological effects of elinzanetant on hypothalamic kisspeptin/neurokinin B/dynorphin neurons.

In postmenopausal women treated with elinzanetant, a transient decrease in luteinizing hormone (LH) levels was observed. No significant changes were noted in oestrogen, follicle-stimulating hormone (FSH), and testosterone levels in this population. These effects are not clinically relevant.

Clinical efficacy and safety

Treatment of moderate to severe VMS associated with menopause (OASIS 1-3)
The efficacy and safety of elinzanetant for the treatment of moderate to severe VMS associated with menopause were studied in 3 randomised, double-blind, placebo-controlled, multicentre phase III studies (OASIS 1, 2 and 3).
In OASIS 1 and 2 a total of 796 postmenopausal women were randomised 1:1 to receive 120 mg elinzanetant 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 VMS, including VMS at night, per week were enrolled in OASIS 1 and 2.
In OASIS 3 a total of 628 postmenopausal women were randomised 1:1 to receive 120 mg elinzanetant or placebo once daily at bedtime for 52 weeks. Inclusion did not require minimum number of VMS.

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 years). Most women were White (80.4%), 17.1% Black or African American, 0.5% Asian, and 8.5% with Hispanic or Latino ethnicity. The study population included postmenopausal women with spontaneous amenorrhoea for ≥ 12 consecutive months (62.1%), spontaneous amenorrhoea/hysterectomy for ≥ 6 months with FSH > 40 IU/L (29.4%), or uni-/bilateral oophorectomy (20.6%). 31.4% had used prior hormone replacement therapy (HRT).

The primary efficacy endpoints in OASIS 1 and 2 were the mean change in frequency of moderate to severe VMS from baseline to weeks 4 and 12, including day and night VMS measured using hot flash daily diary (HFDD).

In OASIS 1 and 2 the women treated with elinzanetant showed statistically significant reduction in frequency of moderate to severe VMS from baseline to weeks 4 and 12 compared to placebo. Results of the change in mean frequency of moderate to severe VMS over 24 hours from OASIS 1 and 2 are shown in table 2.

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

Parameter	OASIS 1		OASIS 2		Pooled studies (OASIS 1 and 2)	
	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)	Elinzanetant 120 mg (N=399)	Placebo (N=397)
Per 24 hours						
Baseline						
Mean (SD)	13.38 (6.57)	14.26 (13.94)	14.66 (11.08)	16.16 (11.15)	14.02 (9.12)	15.22 (12.63)
Change from baseline to week 4						
LS-mean (SE)	-7.60 (0.43)	-4.31 (0.43)	-8.58 (0.49)	-5.54 (0.49)	-8.05 (0.34)	-4.94 (0.34)
LS-mean difference vs placebo (SE)	-3.29 (0.61)		-3.04 (0.69)		-3.11 (0.48)	
95% CI	-4.47, -2.10		-4.40, -1.68		-4.06, -2.16	
p-value [a]	< 0.0001		< 0.0001		< 0.0001 [b]	
Change from baseline to week 12						
LS-mean (SE)	-8.66 (0.58)	-5.44 (0.59)	-9.72 (0.50)	-6.48 (0.49)	-9.16 (0.39)	-5.97 (0.39)
LS-mean difference vs placebo (SE)	-3.22 (0.81)		-3.24 (0.69)		-3.19 (0.54)	
95% CI	-4.81, -1.63		-4.60, -1.88		-4.26, -2.13	
p-value [a]	< 0.0001		< 0.0001		< 0.0001 [b]	

[a] one-sided p-value (α=0.025)

[b] nominal p-value

CI: confidence interval, LS-mean: least squares mean estimated from a mixed model for repeated measures analysis of covariance, SD: standard deviation, SE: standard error

In OASIS 1 and 2 the women treated with elinzanetant showed statistically significant results compared to placebo for the key secondary endpoints:

- reduction in frequency of moderate to severe VMS from baseline to week 1
- reduction in severity of moderate to severe VMS from baseline to weeks 4 and 12
- improvement in PROMIS SD SF 8b total T-score (sleep disturbances) from baseline to week 12
- improvement in MENQOL total score (menopause-related quality of life) from baseline to week 12.

The results from OASIS 1 and 2 are shown in table 3.

Table 3: Key secondary endpoints (OASIS 1 and 2)

Parameter	OASIS 1		OASIS 2		Pooled studies (OASIS 1 and 2)	
	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)	Elinzanetant 120 mg (N=399)	Placebo (N=397)
Per 24 hours						
Frequency of VMS - baseline						
Mean (SD)	13.38 (6.57)	14.26 (13.94)	14.66 (11.08)	16.16 (11.15)	14.02 (9.12)	15.22 (12.63)
Frequency of VMS - change from baseline to week 1						
LS-mean (SE)	-5.13 (0.33)	-2.68 (0.33)	-4.93 (0.39)	-3.28 (0.39)	-5.01 (0.26)	-2.98 (0.26)
LS-mean difference vs placebo (SE)	-2.45 (0.46)		-1.66 (0.55)		-2.03 (0.37)	
95% CI	-3.36, -1.55		-2.73, -0.58		-2.75, -1.31	
p-value [a]	< 0.0001		0.0013		< 0.0001 [b]	
Severity of VMS - baseline						
Mean (SD) [c]	2.56 (0.22)	2.53 (0.23)	2.53 (0.24)	2.54 (0.24)	2.54 (0.23)	2.53 (0.24)
Severity of VMS - change from baseline to week 4						
LS-mean (SE) [c]	-0.55 (0.04)	-0.17 (0.05)	-0.56 (0.05)	-0.30 (0.05)	-0.55 (0.03)	-0.24 (0.03)
LS-mean difference vs placebo (SE)	-0.38 (0.06)		-0.25 (0.07)		-0.32 (0.05)	
95% CI	-0.51, -0.26		-0.39, -0.11		-0.41, -0.22	
p-value [a]	< 0.0001		0.0002		< 0.0001 [b]	
Severity of VMS - change from baseline to week 12						
LS-mean (SE) [c]	-0.80 (0.06)	-0.33 (0.06)	-0.71 (0.07)	-0.41 (0.06)	-0.80 (0.04)	-0.37 (0.05)
LS-mean difference vs placebo (SE)	-0.47 (0.08)		-0.38 (0.09)		-0.42 (0.06)	
95% CI	-0.64, -0.31		-0.56, -0.20		-0.55, -0.30	
p-value [a]	< 0.0001		< 0.0001		< 0.0001 [b]	
Per 7 days						
PROMIS SD SF 8b total T-score - baseline						
Mean (SD)	61.0 (7.7)	60.2 (7.2)	61.7 (6.2)	60.7 (7.2)	61.4 (7.0)	60.5 (7.2)
PROMIS SD SF 8b total T-score - change from baseline to week 12						
LS-mean (SE)	-10.41 (0.60)	-4.83 (0.62)	-10.28 (0.54)	-5.97 (0.53)	-10.33 (0.40)	-5.39 (0.41)
LS-mean difference vs placebo (SE)	-5.58 (0.82)		-4.32 (0.74)		-4.94 (0.55)	
95% CI	-7.18, -3.98		-5.77, -2.86		-6.02, -3.85	
p-value [a]	< 0.0001		< 0.0001		< 0.0001 [b]	
MENQOL total score - baseline						
Mean (SD)	4.56 (1.27)	4.49 (1.31)	4.48 (1.14)	4.49 (1.17)	4.52 (1.20)	4.49 (1.24)
MENQOL total score - change from baseline to week 12						
LS-mean (SE)	-1.36 (0.08)	-0.94 (0.08)	-1.29 (0.09)	-1.00 (0.08)	-1.32 (0.06)	-0.96 (0.06)
LS-mean difference vs placebo (SE)	-0.42 (0.11)		-0.30 (0.12)		-0.36 (0.08)	
95% CI	-0.64, -0.20		-0.53, -0.07		-0.52, -0.20	
p-value [a]	< 0.0001		0.0059		< 0.0001 [b]	

[a] one-sided p-value (α=0.025)

[b] nominal p-value

[c] reported in scales 1 (mild) to 3 (severe); data from post-hoc analysis using moderate to severe VMS

CI: confidence interval, LS-mean: least squares mean estimated from a mixed model for repeated measures analysis of covariance, MENQOL: menopause-specific quality of life, PROMIS SD SF 8b: patient-reported outcomes measurement information system sleep disturbance short form 8b, SD: standard deviation, SE: standard error

Treatment of moderate to severe VMS caused by adjuvant endocrine therapy (OASIS 4)
The efficacy and safety of elinzanetant for the treatment of moderate to severe VMS caused by adjuvant endocrine therapy were studied in a randomised, double-blind, placebo-controlled, multicentre phase III study (OASIS 4) in women with, or at high risk for, developing hormone-receptor positive breast cancer. A total of 474 women were randomised 2:1 to receive 120 mg elinzanetant or placebo once daily at bedtime for 12 weeks, followed by elinzanetant for 40 weeks, for a total treatment of up to 52 weeks. Of these, 473 women had a history of breast cancer and 1 woman had a high risk of developing breast cancer. Women who had at least 35 moderate to severe VMS, including VMS at night, per week were enrolled in OASIS 4. All women received concurrently adjuvant endocrine therapy with tamoxifen (55.4%) or aromatase inhibitors (44.6% e.g. anastrozole), both with and without the use of GnRH analogues.

The patient demographics were generally balanced between treatment groups. The mean age of women was 51 years (range 28-70 years) with 18 women (3.8%) of 65 years or older. Most women were White (88.2%), 1.5% Black or African American, 0.4% Asian, and 2.5% with Hispanic or Latino ethnicity. The study population included women with prior hysterectomy (12.4%) or prior uni-/bilateral oophorectomy (12.2%).

Of the 474 women, 321 (67.7%) were classified as women of non-child-bearing potential and 153 (32.3%) were classified as women of child-bearing potential (WOCBP). In women classified as WOCBP, the use of a highly effective contraceptive method was required.

The primary efficacy endpoints were the mean change in frequency of moderate to severe VMS from baseline to weeks 4 and 12, including day and night VMS measured using HFDD.

In OASIS 4 the women treated with elinzanetant showed a statistically significant reduction in frequency of moderate to severe VMS from baseline to weeks 4 and 12 compared to placebo with a stable effect up to week 50. Results of the change in mean frequency of moderate to severe VMS over 24 hours from OASIS 4 are shown in table 4.

Table 4: Mean change in frequency of moderate to severe VMS from baseline to weeks 4 and 12 (OASIS 4)

Parameter	**OASIS 4**	
	Elinzanetant 120 mg (N=316)	Placebo (N=158)
Per 24 hours		
Baseline		
Mean (SD)	11.41 (6.89)	11.52 (6.43)
Change from baseline to week 4		
LS-mean (SE)	-6.47 (0.26)	-2.99 (0.36)
LS-mean difference vs placebo (SE)	-3.48 (0.44)	
95% CI	-4.35, -2.61	
p-value [a]	< 0.0001	
Change from baseline to week 12		
LS-mean (SE)	-7.53 (0.25)	-4.16 (0.35)
LS-mean difference vs placebo (SE)	-3.38 (0.43)	
95% CI	-4.21, -2.54	
p-value [a]	< 0.0001	

[a] one-sided p-value (α=0.025)
CI: confidence interval, LS-mean: least squares mean estimated from a mixed model for repeated measures analysis of covariance, SD: standard deviation, SE: standard error

In OASIS 4 the women treated with elinzanetant showed statistically significant results compared to placebo for the key secondary endpoints:

- improvement in PROMIS SD SF 8b total T-score (sleep disturbances) from baseline to week 12
- improvement in MENQOL total score (menopause-related quality of life) from baseline to week 12.

The respective results from OASIS 4 were consistent with the results shown in patients with moderate to severe VMS associated with menopause (OASIS 1 and 2). The results of the key secondary endpoints from OASIS 4 are shown in table 5.

Table 5: Key secondary endpoints (OASIS 4)

Parameter	**OASIS 4**	
	Elinzanetant 120 mg (N=316)	Placebo (N=158)
Per 7 days		
PROMIS SD SF 8b total T-score - baseline		
Mean (SD)	60.60 (6.33)	60.74 (6.80)
PROMIS SD SF 8b total T-score - change from baseline to week 12		
LS-mean (SE)	-10.06 (0.41)	-3.94 (0.57)
LS-mean difference vs placebo (SE)	-6.12 (0.70)	
95% CI	-7.49, -4.75	
p-value [a]	< 0.0001	
MENQOL total score - baseline		
Mean (SD)	4.82 (1.17)	4.77 (1.25)
MENQOL total score - Change from baseline to week 12		
LS-mean (SE)	-1.23 (0.06)	-0.55 (0.08)
LS-mean difference vs placebo (SE)	-0.68 (0.10)	
95% CI	-0.88, -0.48	
p-value [a]	< 0.0001	

[a] one-sided p-value (α=0.025)

CI: confidence interval, LS-mean: least squares mean estimated from a mixed model for repeated measures analysis of covariance, MENQOL: menopause-specific quality of life, PROMIS SD SF 8b: patient-reported outcomes measurement information system sleep disturbance short form 8b, SD: standard deviation, SE: standard error

Endometrial safety

Endometrial safety of elinzanetant was assessed primarily in the clinical study OASIS 3 by transvaginal ultrasound and 142 endometrial biopsies collected at 52 weeks of treatment with elinzanetant. Transvaginal ultrasound did not reveal increased endometrial thickness. There were no cases of endometrial hyperplasia or malignancy based on endometrial biopsies.

Breast safety

In the OASIS 4 clinical study up to week 52, the reported recurrence rate of breast cancer was 0.4% in patients using tamoxifen and 1.9% in patients using aromatase inhibitors compared to 3.4% and 2.1%, respectively, in the published literature.

Bone safety

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Lynkuet in all subsets of the paediatric population for the treatment of moderate to severe VMS associated with menopause or caused by adjuvant endocrine therapy related to breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Elinzanetant soft gel capsules show a dose-proportional increase in C_{max} in the dose range 25 mg to 600 mg. The AUC increases dose-proportional in the dose range 25 mg to 120 mg and greater than dose proportional in the dose range 160 mg to 600 mg.
Steady state plasma concentrations of elinzanetant were reached 5 – 7 days after daily dosing, with < 2-fold accumulation.

Absorption

The absolute bioavailability of elinzanetant is 52%.
Administering 120 mg elinzanetant with food reduces C_{max} with 60-70% and the $AUC_{(0-24)}$ with 20-40%, but no effect on the AUC was observed. The t_{max} shifted from 1-1.5 hours under fasted conditions to 3-4 hours under fed conditions. The food effect is not expected to be of clinical relevance for efficacy. Lynkuet may be administered with or without food (see section 4.2).

Distribution

The plasma protein binding of elinzanetant is high (> 99%) and is affected by circadian fluctuation. The blood-to-plasma ratio is between 0.6 and 0.7. The mean volume of distribution after intravenous administration at steady state (V_{ss}) of elinzanetant is 137 L, indicating extensive extravascular distribution. Exposure of elinzanetant in human brain was shown by clinical positron emission tomography (PET) studies.

Biotransformation

Elinzanetant is primarily metabolised by CYP3A4 to yield 3 active metabolites (M30/34 [13.7%], M27 [7.6%], M18/21 [4.9%]). Elinzanetant is also metabolised to a minor extend by CYP3A5 and UGTs. The active metabolites have similar potency for the human NK-1 and NK-3 receptors as compared to elinzanetant and contribute for < 50% to the pharmacological effect. The ratio of these metabolites to parent in plasma is approximately 0.39.

Elimination

Elinzanetant is mainly eliminated by metabolism. The clearance of elinzanetant after single intravenous dose is 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 is approximately 45 hours in women with VMS after multiple dose and 11.2 to 33.8 hours in healthy volunteers after single dose.

Transporter

Elinzanetant is *in vitro* a substrate for the P-glycoprotein (P-gp) transporter protein. No clinically relevant interaction with P-gp inhibitors and inducers is expected due to high permeability of elinzanetant through membranes and its main elimination through metabolism.

Hepatic impairment

In a clinical pharmacokinetic study, 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 healthy volunteers 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 patients 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.

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

Effects of age, race, and body weight

There are no clinically relevant effects on age (22 to 75 years), race (White, Black or African American, Asian), and body weight (45 to 129 kg) on the pharmacokinetics of elinzanetant.

Inhibition and induction potential towards enzymes and transporters

In vitro studies indicated that at maximal intestinal concentrations elinzanetant is an inhibitor of CYP3A4 and the transporters P-glycoprotein (P-gp) and BCRP. At maximal portal vein concentrations, elinzanetant is an inhibitor of OATP1B1 and 1B3. At maximal systemic concentrations, elinzanetant is a direct and time-dependent inhibitor of CYP3A4 and an inhibitor of the transporters P-gp, BCRP, OATP1B3, and MATE1. Elinzanetant is not an inducer via AhR, CAR, or PXR at clinically relevant concentrations.
Clinical studies were performed investigating the inhibition potential of elinzanetant towards CYP3A4 (single and repeated dosing with elinzanetant) and the transporters P-gp (dabigatran etexilate) and BCRP, OATP1B1 and 1B3 (rosuvastatin). Elinzanetant is a weak inhibitor of CYP3A4 using midazolam as index substrate (C_{max} increased 1.1- to 1.5-fold and AUC increased 1.4- to 1.8-fold). Elinzanetant did not affect the PK of dabigatran etexilate which was used as reference substrate of P-gp. Elinzanetant increased the PK of rosuvastatin (substrate of BCRP, OATP1B1 and 1B3) 1.2- to 1.3-fold.
No dedicated clinical DDI study was conducted towards MATE1. However, no effect on creatinine clearance was observed in a clinical study at supratherapeutic dosages of 600 mg. Overall, this indicates that the observed *in vitro* interaction potential is clinically not relevant.
In study OASIS 4, sparse blood samples were collected and concentrations of tamoxifen and its metabolites (N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen) were investigated. No effect on the steady state plasma concentrations of tamoxifen and its metabolites were observed when co-administered with elinzanetant.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, phototoxicity, genotoxicity and abuse potential.

Systemic toxicity

Repeated dose toxicity studies were conducted in rats and cynomolgus monkeys.
In female rats, daily administration of elinzanetant for 4 weeks at doses representing 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 representing 4-fold (males) or 7-fold (females) the $AUC_{(0-24)}$ at the human therapeutic dose led to involuntary muscle contractions from day 24 in 10/88 animals, which later had also convulsions from day 34. In the same study, daily administration of elinzanetant at doses representing equal to or greater than 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 representing equal to or greater than 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, administration of elinzanetant at 80 mg/kg/day showed diarrhoea. Diarrhoea was not observed at a lower dose of 60 mg/kg/day despite the 1.8-fold higher systemic exposure.

Embryotoxicity / Teratogenicity / Reproduction toxicity

In the embryo-foetal developmental studies with elinzanetant in rats and rabbits no evidence of embryo-foetal toxicity occurred at doses resulting in exposures 16-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 percentage of pre-implantation and post-implantation embryo loss, resulting in reduced litter size, and lower foetal body weights were seen at the dose resulting in 16-fold the $AUC_{(0-24)}$ at the human therapeutic dose. These effects were not observed following dosing resulting in 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 resulting in 23-fold the $AUC_{(0-24)}$ at the human therapeutic dose (safety margin 6.7-fold at the NOAEL). Increase in total litter loss and corresponding decrease of pup viability on post-natal day 5 was 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.

In rats, a reduction in milk production of dams was seen at clinically relevant doses.

Carcinogenicity

In a 2-year carcinogenicity study on elinzanetant in rats an increase in uterine neoplasms and lymphomas was reported. The findings were seen at a dose 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 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.

No drug-related neoplasms were observed up to the highest dose of 3-fold (males) or 2-fold (females) the $AUC_{(0-24)}$ at the human therapeutic dose in the 26-week carcinogenicity study on elinzanetant in transgenic mice.

Environmental risk assessment (ERA)

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling

All-rac-α-tocopherol (E 307)
Caprylocaproyl macrogolglycerides
Glycerol monocaprylocaprate
Glycerol mono-oleate (E 471)
Polysorbate 80 (E 433)

Capsule shell

Gelatin
Sorbitol, liquid, partially dehydrated (E 420) - glycerol (E 422) blend
Iron oxide red (E 172)
Iron oxide yellow (E 172)
Medium-chain triglycerides
Phosphatidyl choline solution 53% in medium-chain triglycerides
Titanium dioxide (E 171)

Printing ink

Macrogol 400 (E 1521)
Polyvinyl acetate phthalate
Propylene glycol (E 1520)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

PVC/PCTFE-Aluminium/PET/paper blister containing 12 soft capsules (6 × 2 as unit dose).
Each pack contains 24 or 60 soft capsules.
Each multipack contains 180 (3 packs of 60) soft capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1991/001 - Lynkuet 60 mg - 24 soft capsules
EU/1/25/1991/002 - Lynkuet 60 mg - 60 soft capsules
EU/1/25/1991/003 - Lynkuet 60 mg - 180 soft capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 November 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Catalent Germany Eberbach GmbH
Gammelsbacher Str. 2
69412 Eberbach
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - MULTI-PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lynkuet 60 mg soft capsules
elinzanetant

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains 60 mg elinzanetant.

3. LIST OF EXCIPIENTS

Contains sorbitol. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Soft capsule (capsule)

Multipack: 180 (3 packs of 60) soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Do not cut, chew or crush the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/25/1991/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lynkuet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – INTERMEDIATE PACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lynkuet 60 mg soft capsules
elinzanetant

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains 60 mg elinzanetant.

3. LIST OF EXCIPIENTS

Contains sorbitol. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Soft capsule (capsule)

Part of a 3-month pack, contains 60 soft capsules. Not for individual sale.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Do not cut, chew or crush the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/25/1991/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lynkuet

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Lynkuet 60 mg soft capsules
elinzanetant

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains 60 mg elinzanetant.

3. LIST OF EXCIPIENTS

Contains sorbitol. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Soft capsule (capsule)

24 soft capsules
60 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Do not cut, chew or crush the capsules.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/25/1991/001
EU/1/25/1991/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lynkuet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT-DOSE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lynkuet 60 mg capsules
elinzanetant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lynkuet 60 mg soft capsules
elinzanetant

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lynkuet is and what it is used for

Lynkuet contains the active substance elinzanetant. It is a non-hormonal medicine.

It is used to treat **moderate to severe vasomotor symptoms**:
- associated with menopause
- caused by so-called adjuvant endocrine therapy for breast cancer.
  These are anti-hormonal medicines (such as tamoxifen or anastrozole) that prevent cancer from coming back after anti-cancer treatment.

Vasomotor symptoms are sudden feelings of warmth or intense heat, mainly in the face, neck and chest and sweating during day or night, also called hot flashes or night sweats.

How Lynkuet works
The active substance in Lynkuet, elinzanetant, works by blocking the activity of certain nerve cells in the brain (so-called Kisspeptin/Neurokinin B/Dynorphin neurons) that are involved in regulating body temperature and sleep. By blocking these nerve cells, Lynkuet helps to control hot flashes and night sweats.

2. What you need to know before you take Lynkuet

Do not take Lynkuet if
- you are allergic to elinzanetant or any of the other ingredients of this medicine (listed in section 6)
- you are pregnant or think you might be pregnant.

Warnings and precautions
Talk to your doctor or pharmacist before taking Lynkuet, if
- you are taking certain medicines that keep the CYP3A4 liver enzyme from working properly. These medicines may cause Lynkuet to stay longer in your body, which may increase the risk of side effects. Examples are medicines used to treat infections such as itraconazole, clarithromycin, ritonavir, cobicistat or to treat breast cancer such as ribociclib.
- you are taking hormone replacement therapy with oestrogens (medicines used to treat oeastrogen deficiency symptoms).

If you are unsure if you are taking such medicines, talk to your doctor.

Children and adolescents
This medicine is not for use in children and adolescents under 18 years.

Other medicines and Lynkuet
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained with or without prescription, or over the counter medicines such as vitamins, dietary supplements or herbal medicines.

Certain medicines may influence how Lynkuet works, or Lynkuet may influence how these medicines work. These may include medicines to:
- treat fungal or bacterial infections such as itraconazole, clarithromycin, erythromycin, ciprofloxacin, fluconazole
- treat HIV infections such as ritonavir, cobicistat
- treat breast cancer such as ribociclib
- treat high blood pressure, chest pain and fast heartbeat such as verapamil
- prevent organ rejection after transplantation such as cyclosporine, tacrolimus
- treat long-term pain such as fentanyl

Lynkuet with food and drink
Do not eat grapefruit or drink grapefruit juice as long as you take this medicine. This is because grapefruit also keeps the CYP3A4 enzyme from working properly and may cause Lynkuet to stay longer in your body. This may increase the risk of side effects.

Pregnancy and breast-feeding
Do not take this medicine if you are pregnant, or if you think you might be pregnant.
If you could get pregnant, you or your partner should use an effective birth control method to prevent pregnancy while you are taking this medicine. Ask your doctor about the best method of birth control for you.
If you get pregnant while taking this medicine, stop taking it and talk to your doctor.
If you are breast-feeding or plan to breast feed, ask your doctor for advice before taking this medicine.

Driving and using machines
If you feel tired or sleepy while you are taking this medicine take extra care when driving or using machines.

Lynkuet contains sorbitol
This medicine contains 71 mg sorbitol in each capsule. Sorbitol is a source of fructose. Sorbitol may change how well other oral medicines work when you take them at the same time.

3. How to take Lynkuet

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You should take one dose (2 capsules) of this medicine each day at bedtime.

Talk with your doctor, if
- you take this medicine together with other medicines
- you have kidney problems

Your doctor may reduce your daily dose to only 1 capsule each day at bedtime.

Swallow the capsule(s) whole with a glass of water. Do not cut, chew or crush the capsule(s) due to its oily formulation.

If you take more Lynkuet than you should
Taking too much Lynkuet may make side effects more likely or more severe. Talk to your doctor or pharmacist if you have taken too much of this medicine.

If you forget to take Lynkuet
If you missed a dose at bedtime, take the next dose as planned on the following day. Do not take a double dose to make up for a forgotten dose.

If you stop taking Lynkuet
Do not stop taking Lynkuet unless your doctor tells you to do so. If you want to stop taking this medicine before finishing treatment, talk to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In patients with moderate to severe vasomotor symptoms associated with menopause, the following side effects were seen:

Common (may affect up to 1 in 10 people)
- abdominal pain
- diarrhoea
- dizziness
- tiredness
- headache
- muscle spasms
- skin rash
- sleepiness

Uncommon (may affect up to 1 in 100 people)
- increase in levels of certain liver enzymes (ALT or AST)
- increased sensitivity of the skin to sun

In patients with moderate to severe vasomotor symptoms caused by adjuvant endocrine therapy , the following side effects were seen:

Very common (may affect more than 1 in 10 people)
- tiredness

Common (may affect up to 1 in 10 people)
- depression, depressive mood
- diarrhoea
- increase in levels of certain liver enzymes (ALT)
- dizziness
- hair loss
- muscle spasms
- sleepiness
- spinning sensation

Uncommon (may affect up to 1 in 100 people)
- increase in levels of certain liver enzymes (AST)
- increased sensitivity of the skin to sun

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lynkuet

Keep this medicine out of the sight and reach of children.

This medicine does not require any special temperature storage conditions. Store in the original blister in order to protect from moisture.

Do not use this medicine after the expiry date which is stated on the carton and on each blister after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lynkuet contains
- The active substance is elinzanetant. Each soft capsule contains 60 mg of elinzanetant.
- The other ingredients are all-rac-α-tocopherol (E 307), caprylocaproyl macrogolglycerides, gelatin, glycerol monocaprylocaprate, glycerol mono-oleate (E 471), iron oxide red (E 172), iron oxide yellow (E 172), macrogol 400 (E 1521), medium-chain triglycerides, partially dehydrated liquid sorbitol (E 420) - glycerol (E 422) blend, phosphatidyl choline solution 53% in medium-chain triglycerides, polysorbate 80 (E 433), polyvinyl acetate phthalate, propylene glycol (E 1520), titanium dioxide (E 171).

See ‘Lynkuet contains sorbitol’ in section 2 for more information.

What Lynkuet looks like and contents of the pack
The soft capsules (capsules) are opaque red and oblong. They are marked with white printing of “EZN60”.
They are available in PVC/PCTFE-Aluminium/PET/paper blisters in cartons of 24 or 60 or as multipack with 180 (3 packs of 60) soft capsules. Each blister contains 6 × 2 capsules as unit dose.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Catalent Germany Eberbach GmbH
Gammelsbacher Str. 2
69412 Eberbach
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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