AusPAR – Lynkuet – elinzanetant – Bayer Australia Ltd – PM-2024-03648-1-5 Final – 2 March 2026. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi**>**

▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – LYNKUET® (ELINZANETANT)

1 NAME OF THE MEDICINE

elinzanetant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 60 mg of elinzanetant

Excipient with known effects: soya bean products

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Opaque red, oblong soft capsules, size 20 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 Pharmacodynamic properties – Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

For oral use.

The capsules should be swallowed whole with water. The capsules should not be cut, chewed or crushed.

The recommended daily dose is 120 mg elinzanetant (two 60 mg capsules) taken orally once daily at bedtime.
The capsules can be taken with or without food.

The benefit and duration of treatment with LYNKUET should be periodically assessed based on the natural history and course of the vasomotor symptoms (VMS) associated with menopause. No clinical data beyond a treatment period of 12 months are available (see Section 5.1 Pharmacodynamic Properties – Clinical Trials).

OFFICIAL

Liver function testing is recommended before starting treatment with elinzanetant. Liver function testing should be performed if symptoms suggestive of liver injury occur (see Section 4.4 Special warnings and precautions for use).

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 Interactions with other medicines and other forms of interactions). After discontinuation of the moderate inhibitor (after 3 to 5 half-lives of the inhibitor), LYNKUET should be used at the usual dose of 120 mg once daily.

Use in hepatic impairment
No clinically relevant increase in elinzanetant exposure was observed in patients with mild chronic hepatic impairment. In a clinical pharmacokinetic study, moderate hepatic impairment increased the exposure of elinzanetant and no clinical data are available in these patients. Elinzanetant has not been studied in individuals with severe chronic hepatic impairment (see Section 5.2 Pharmacokinetic properties).
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.

Elinzanetant is contraindicated for use in individuals with severe (Child-Pugh C) chronic hepatic impairment (see Section 4.3 Contraindications).

Use in 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 Pharmacokinetic properties). 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 or moderate (eGFR 30 to 89 ml/min/1.73m^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.

Use in the elderly
The safety and efficacy of elinzanetant has not been established in women over 65 years of age.

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

OFFICIAL

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

4.3 CONTRAINDICATIONS

LYNKUET is contraindicated in:

- Patients with known hypersensitivity to elinzanetant or to any of the excipients in the formulation (see Section 6.1 List of excipients).
- Concomitant use of strong CYP3A4 inhibitors (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).
- Patients with pre-existing Class C (severe) chronic hepatic impairment (see Section 4.4 Special warnings and precautions for use).
- Known or suspected pregnancy (see Section 4.6 Fertility, pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant use with other medicinal products
CYP3A4 inhibitors may decrease the clearance of elinzanetant, resulting in higher exposure:

- Strong CYP3A4 inhibitors: The concomitant use of LYNKUET with strong CYP3A4 inhibitors is contraindicated (see Sections 4.3 Contraindications and 4.5 Interactions with other medicines and other forms of interactions).
- Moderate CYP3A4 inhibitors: Reduce LYNKUET dosage when co-administered with moderate CYP3A4 inhibitors (see Sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions).

Moderate to strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, St. John's Wort) reduce elinzanetant exposure and efficacy may be reduced. Monitor elinzanetant efficacy when co-administered with moderate to strong CYP3A4 inducers (see Section 4.5 Interactions with other medicines and other forms of interactions).

Liver Safety
Hepatotoxicity has been reported with the use of a different NK-3 receptor antagonist.

In the clinical studies with elinzanetant, there have been no indications of hepatotoxicity so far. However, due to the limited number of patients who have been treated with elinzanetant in clinical studies, any rare hepatic adverse effects cannot be completely excluded.

Liver function testing is recommended before starting treatment with elinzanetant. Liver function testing should be performed if symptoms suggestive of liver injury occur.

Patients with Impaired Liver Function
The use of LYNKUET is not recommended for patients with moderate (Child-Pugh B) chronic hepatic impairment. If such patients are still treated with LYNKUET, the liver function must be closely monitored (see Section 4.2 Dose and method of administration).

Elinzanetant is contraindicated for use in individuals with severe (Child-Pugh C) chronic hepatic impairment (see Section 4.3 Contraindications).

Oestrogen-dependent tumours
The efficacy and safety of LYNKUET in patients with breast cancer or other oestrogen dependent tumours or patients with a history of such malignancies has not been established. This applies, in particular, to patients receiving anti-oestrogen treatment which is associated with severe VMS and/or other symptoms of oestrogen deficiency.

The decision to use LYNKUET 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.

Pharmacologically induced menopause
The use of elinzanetant has only been investigated in patients with natural or surgical menopause. No data for use of elinzanetant in patients with pharmacologically induced menopause (e.g. in those treated with GnRH analogues) are available.

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

Concomitant use of hormone replacement therapy with oestrogens (local vaginal preparations excluded)
Concomitant use of elinzanetant and systemic hormone replacement therapy with oestrogens has not been studied, and therefore concomitant use is not recommended.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on elinzanetant
Elinzanetant is metabolised via Cytochrome P450 isoform 3A4 (CYP3A4) and is a substrate for the P-glycoprotein (P-gp) transporter protein.

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

- **Strong CYP3A4 inhibitors**

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.

The concomitant use of LYNKUET with strong CYP3A4 inhibitors is contraindicated (see Section 4.3 Contraindications).

OFFICIAL

- **Moderate CYP3A4 inhibitors**

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 modelling predictions after co-administration of 60 mg elinzanetant with moderate CYP3A4 inhibitor erythromycin showed a 1.4-fold increase of AUC and no increase for C_{max} compared to 120 mg elinzanetant alone.

With co-administration of a moderate CYP3A4 inhibitor (e.g. erythromycin, ciprofloxacin, fluconazole and verapamil), the recommended daily dose of LYNKUET is 60 mg (see Section 4.2 Dose and method of administration).

- **Weak CYP3A4 inhibitors**

PBPK modelling 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.

- **P-gp inhibitors**

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

- **Grapefruit juice**

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

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.

Due to the reduction in exposure efficacy may be reduced. Monitor the efficacy of LYNKUET when co-administered with moderate to strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, St. John's Wort).

Effects of elinzanetant on other medicinal products
In vitro, elinzanetant has been shown to be a CYP3A4 inhibitor, CYP3A4 inducer, as well as an inhibitor of BCRP, P-gp und OATP1B3, and may affect the exposure of medicines that are mainly eliminated via CYP3A4, BCRP, P-gp, or OATP1B3. *In vivo*, no clinically relevant inhibition of BCRP, P-gp and OATP1B1/OATP1B3 was observed.

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. ciclosporin, fentanyl, or tacrolimus). The related recommendation in the product information of these CYP3A4 substrates should be followed.

OFFICIAL

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

Effects on fertility

No human data on the effect of LYNKUET on fertility are available. Elinzanetant did not affect the incidence of pregnancy in female rats at oral doses up to 100 mg/kg/day (estimated to yield exposure [plasma AUC] 16-times higher than in patients at the clinical dose of 120 mg/day); adverse effects on early embryonic development (increased pre- and post-implantation loss) were observed at this highest dose though.

Use in pregnancy – Pregnancy Category B3

The use of LYNKUET in pregnant women is not indicated.

There are no data on the use of LYNKUET in pregnant women. Studies in animals indicate the potential for reproductive and developmental toxicity in pregnant patients.

Elinzanetant reduced perinatal survival of the offspring in rats at oral doses ≥5 mg/kg/day, yielding exposure equivalent to that of patients at the recommended dose. Increased post-implantation loss, delayed parturition, dystocia, increased stillbirths and decreased pup body weight were observed in rats at 100 mg/kg/day. No malformations were observed in rats or rabbits up to the highest doses tested (100 and 140 mg/kg/day in the respective species, yielding exposure 23- and 1.2-times higher than in patients).

Elinzanetant and/or its metabolites were shown to cross the placenta in rats.

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.

Use in lactation

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. Levels of elinzanetant in milk were higher than in plasma. Use of LYNKUET in lactating women is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Women should be advised to be careful when driving or using machines if they experience fatigue, dizziness or somnolence during treatment with LYNKUET (see Section 4.8 Adverse effects (Undesirable effects)).

Driving ability study

Driving performance was assessed at 9 hours after bedtime administration of LYNKUET 120 mg and 240 mg (two times the recommended dose) in a randomised, double-blind, placebo- and

OFFICIAL

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 LYNKUET 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 1 day but not after 5 consecutive days of LYNKUET administration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

The overall safety profile of LYNKUET is based on data from 1113 treated women with VMS associated with menopause, who received at least one dose of elinzanetant 120 mg, in phase III (OASIS 1, OASIS 2, OASIS 3) and phase II (SWITCH-1) clinical studies.

The most frequently observed adverse drug reactions (≥5%) with elinzanetant were headache and fatigue.

Adverse events

Table 1. OASIS 1, 2 and 3, SWITCH-1: treatment-emergent adverse events reported in at least 1% in LYNKUET after 12 weeks of treatment

Preferred Term	Elinzanetant 120 mg	Placebo
Abdominal pain upper	11 (1.4%)	3 (0.4%)
Alopecia	12 (1.6%)	6 (0.8%)
Arthralgia	23 (3.0%)	20 (2.7%)
Back pain	11 (1.4%)	6 (0.8%)
Blood creatine phosphokinase increased	9 (1.2%)	6 (0.8%)
Constipation	9 (1.2%)	7 (0.9%)
Depressed mood	10 (1.3%)	1 (0.1%)
Diarrhoea	16 (2.1%)	14 (1.9%)
Dizziness	23 (3.0%)	8 (1.1%)
Dry mouth	11 (1.4%)	6 (0.8%)
Fatigue	41 (5.4%)	10 (1.3%)
Gastrooesophageal reflux disease	15 (2.0%)	5 (0.7%)
Headache	57 (7.5%)	32 (4.2%)
Muscle spasms	11 (1.4%)	3 (0.4%)
Nasopharyngitis	14 (1.8%)	12 (1.6%)
Nausea	19 (2.5%)	14 (1.9%)
Rash	10 (1.3%)	6 (0.8%)
Somnolence	26 (3.4%)	4 (0.5%)

OFFICIAL

Tabulated list of adverse reactions

The adverse drug reactions observed during clinical studies in women treated with LYNKUET are listed in Table 2.

They are classified according to System Organ Class (MedDRA). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug 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.

Table 2. Adverse reactions reported for elinzanetant 120mg

MedDRA System Organ Class	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 papular, rash pruritic
[f] Including muscle tightness, 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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There were no cases of overdose reported in pre-market clinical trials. Single doses of LYNKUET up to 600 mg have been tested in clinical studies in healthy volunteers. Adverse events 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.

OFFICIAL

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Elinzanetant is a non-hormonal, selective neurokinin 1 (NK_1) and 3 (NK_3) receptors antagonist that 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 estrogen decline in menopause.

Elinzanetant has high affinity for human NK_1 receptors (pKi values of 8.7 to 10.2) and NK_3 receptors (pKi values 8.0 to 8.8), and not for human NK_2 receptors (as shown by a low pKi 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 5 times the maximum recommended dose.

Clinical trials

The efficacy and safety of elinzanetant for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause were demonstrated in two similar randomised, double-blind, placebo-controlled, multi-centre Phase III studies (OASIS 1 and 2).

A total of 796 postmenopausal women were randomised 1:1 to receive elinzanetant or placebo once daily at bedtime for 12 weeks, followed by elinzanetant in all patients for 14 weeks, for a total treatment of up to 26 weeks. Women who had at least 50 moderate to severe hot flashes (HFs), including night-time HFs, per week were enrolled in OASIS 1 and 2.

In OASIS 1 and 2 studies, the mean age of women was 54.6 years (range 40-65). 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 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 HFs measured using Hot Flash Daily Diary (HFDD).

OFFICIAL

The key secondary endpoints were mean change in severity of moderate to severe HF from baseline to Week 4 and 12 and the mean change in frequency of moderate to severe HFs from baseline to Week 1 using HFDD, the mean change in the Patient-Reported Outcome (PRO) instruments PROMIS SD SF 8b to assess sleep disturbances total T-score and MENQOL total score to evaluate menopause-related quality of life from baseline to Week 12.

In OASIS 1 and 2, the elinzanetant treatment groups showed a statistically significant and clinically meaningful reduction in frequency of moderate to severe HFs 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 HFs from baseline to weeks 4 and 12 compared to placebo.
A statistically significant improvement in frequency of moderate to severe HFs was observed at Week 1 with elinzanetant.

Results of the change in mean frequency and severity of moderate to severe HFs over 24 hours from OASIS 1 and OASIS 2 are shown in Table 3.

Table 3: Mean change in frequency and severity of moderate to severe HFs from baseline to Weeks 1, 4 and 12 (OASIS 1 and 2)

Parameter	**OASIS 1**			**OASIS 2**		
	LYNKUET 120 mg (N= 199)	**Placebo (N= 197)**	**Difference LYNKUET - placebo 95% CI p-value***	**LYNKUET 120 mg (N= 200)**	**Placebo (N= 200)**	**Difference LYNKUET - placebo 95% CI p-value***
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 1** LS-Means (SE)	-5.13 (0.33)	-2.68 (0.33)	-2.45 (0.46) -3.36, -1.55 <0.0001	-4.93 (0.39)	-3.28 (0.39)	-1.66 (0.55) -2.73, -0.58 0.0013
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
* - one-sided p-value
** - key secondary endpoint

OFFICIAL

The results in reduction of frequency and severity of moderate to severe HFs were consistent across the patient subgroups based on race, ethnicity, BMI and smoking status.

In OASIS 1 and 2 women treated with elinzanetant showed a statistically significant improvement in sleep disturbances from baseline to Week 12 compared to placebo as assessed by the PROMIS SD SF 8b total T-score. Women treated with elinzanetant showed a statistically significant improvement in menopause related quality of life from baseline to Week 12 as assessed by the MENQOL total score.

Table 4: PROMIS SD SF 8b total T-score and MENQOL total score change from baseline at Week 12 (OASIS 1 and 2)

	OASIS 1			**OASIS 2**		
Parameter	**LYNKUET 120 mg (N= 199)**	**Placebo (N= 197)**	**Difference LYNKUET - placebo (95% CI) P-value***	**LYNKUET 120 mg (N= 200)**	**Placebo (N= 200)**	**Difference LYNKUET - placebo 95% CI P-value***
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)**	
Change from baseline to week 12 LS-Means (SE)	-10.41 (0.60)	-4.83 (0.62)	-5.58 (0.82) -7.18, -3.98 <0.0001	-10.28 (0.54)	-5.97 (0.53)	-4.32 (0.74) -5.77, -2.86 <0.0001
MENQOL total score **Baseline** Mean (SD)	4.56 (1.27)	4.49 (1.31)		4.48 (1.14)	4.49 (1.17)	
Change from baseline to week 12 LS-Means (SE)	-1.36(0.08)	-0.94 (0.08)	-0.42 (0.11) -0.64, -0.20 <.0001	-1.29 (0.09)	-1.00 (0.08)	-0.30 (0.12) -0.53, -0.07 0.0059

CI = Confidence Interval, LS-Means = Least Squares Means, MENQOL =- Menopause Specific Quality of Life Scale, PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b

*- one-sided p-value

The OASIS 3 study was a supportive, randomised, double-blind, placebo-controlled, multi-centre Phase III study with a primary efficacy endpoint of mean change in frequency of moderate to severe HFs 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). The study did not contain a HF severity endpoint, and no minimum disease severity was required as an inclusion criterion. Elinzanetant showed a statistically significant outcome on the primary HF frequency endpoint with a stable effect as evaluated up to Week 50 based on descriptive statistics.

Endometrial safety

Endometrial safety of LYNKUET was assessed in clinical studies OASIS 1, 2 and 3 by transvaginal ultrasound and endometrial biopsies. Transvaginal ultrasound did not reveal increased endometrial thickness. There were no cases of endometrial hyperplasia or malignancy based on endometrial biopsies.

OFFICIAL

Bone safety

Bone safety of LYNKUET 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 LYNKUET was comparable to that with placebo and was within the expected age-related changes per year.

5.2 PHARMACOKINETIC PROPERTIES

In healthy volunteers, elinzanetant C_{max} and AUC increased in greater than dose-proportional manner (20% to 50%) over the dose range from 40 to 160 mg once daily (0.33 to 1.33 times the recommended dose). Steady state plasma concentrations of elinzanetant were reached 5 to 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} is 1.0 (1 to 4) hour. 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 (Vss) of elinzanetant is 137 L, indicating extensive extravascular distribution. The plasma protein binding of elinzanetant is very high (99.7%). 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.

Metabolism

Elinzanetant is primarily metabolised by CYP3A4 to yield three active metabolites. These metabolites have roughly similar affinity 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.

Excretion

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 effective half-life of elinzanetant is approximately 45 hours in women with vasomotor symptoms.

Special populations

Hepatic impairment

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

OFFICIAL

Child-Pugh Class B (moderate) chronic hepatic impairment, the mean elinzanetant C_{max} and $AUC_{(0-24)}$ increased 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, the mean elinzanetant $C_{max, unbound}$ increased 2.3-fold and $AUC_{unbound}$ increased 2.2-fold. In patients with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment, the mean elinzanetant $C_{max, unbound}$ and $AUC_{unbound}$ increased 1.9-fold.

A population pharmacokinetic analysis of the clinical study data indicates a 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).

5.3 PRECLINICAL SAFETY DATA

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 test.

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.

OFFICIAL

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 unbound clinical C_{max} at the clinical dose of 120 mg/day. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule filling
dl-alpha-tocopherol
Caprylocaproyl macrogolglycerides
Glyceryl mono and dicaprylocaprate
Glyceryl monooleate
Polysorbate 80

Capsule shell
Gelatin
Partially dehydrated liquid sorbitol
Glycerol
Iron oxide red
Iron oxide yellow
Titanium dioxide
Opacode WB water based Monogramming Ink NSP-78-18022 White

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store capsules in original pack until required.

6.5 NATURE AND CONTENTS OF CONTAINER

The capsules are packed in Alu/ Aclar blisters.

Pack sizes: 24 (sample), 60, 180

Some pack sizes may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

OFFICIAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

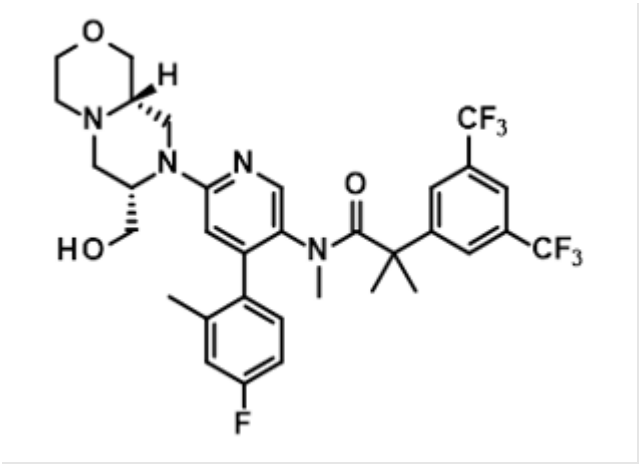
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical name : 2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]pyridin-3-yl}-N,2-dimethylpropanamide

Empirical formula : $C_{33}H_{35}F_7N_4O_3$

Molecular weight : 668.7 g/mol



CAS number

929046-33-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – PRESCRIPTION ONLY MEDICINE

8 SPONSOR

BAYER AUSTRALIA LTD
ABN 22 000 138 714
875 Pacific Highway
Pymble NSW 2073
www.bayer.com.au

9 DATE OF FIRST APPROVAL

11 September 2025

AusPAR – Lynkuet – elinzanetant – Bayer Australia Ltd – PM-2024-03648-1-5 Final – 2 March 2026. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-pi**>**

10 DATE OF REVISION

n/a

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New Product Information

® Registered Trademark of the Bayer Group, Germany

OFFICIAL