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

Etcamah 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of camizestrant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Beige, round, bi-convex, film-coated tablet, debossed with 'CM' above '75' on one side and plain on the reverse. Approximate diameter: 9 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Etcamah in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of *ESR1*-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor (for biomarker based patient-selection, see section 4.2 and 5.1).

In pre- or peri-menopausal women and in men, Etcamah plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist or antagonist.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Patient selection

Patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer on first-line endocrine treatment should be selected for treatment based on the presence of *ESR1*-mutations in plasma or tumour specimen collected every 3 months until an *ESR1*-mutation has been detected, and which should be assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose (see section 5.1). If a CE-marked IVD is not available, an alternative validated test should be used.

Posology

The recommended dose of Etcamah in combination with a CDK4/6 inhibitor is 75 mg once daily. The CDK4/6 inhibitor should be continued at the same dose at the time of initiation with Etcamah as when the *ESR1*m was detected.

Please also refer to the summary of product characteristics (SmPC) of the CDK4/6 inhibitor or LHRH agonist or antagonist for the recommended dosing information. If the CDK4/6 inhibitor is permanently discontinued, Etcamah should also be discontinued.

Treatment duration
Treatment with Etcamah should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Missed dose
If a dose of Etcamah is missed, it can be taken immediately within 6 hours after the time it is usually taken. After more than 6 hours, the dose should be skipped for that day. The next dose of Etcamah should be taken at the usual time.

Vomiting
If the patient vomits, an additional dose should not be taken. The next dose of Etcamah should be taken at the usual time.

Monitoring for Etcamah in combination with CDK4/6 inhibitors
For the combination of Etcamah with a CDK4/6 inhibitor, ECG should be assessed before initiating treatment, at approximately day 8 and day 15 of the first cycle, and then as clinically indicated. Thereafter, monitoring during combination treatment should be performed according to the recommendations in the SmPC of the co-administered CDK4/6 inhibitor. In case of QTc prolongation during treatment, more frequent ECG monitoring is recommended.

In addition, for the combination of Etcamah with ribociclib, treatment should be initiated only in patients with QTcF values less than 450 msec, and analysis of electrolytes should be performed before initiating combination treatment, at day 15 and as clinically indicated. Refer to the ribociclib SmPC for dose modification guidelines and other relevant safety information.

Dose adjustments
Treatment with Etcamah may be temporarily interrupted and/or discontinued to manage adverse reactions per dose modification guideline provided in Table 1.

Table 1 Recommended dose modification for Etcamah

NCI CTCAE (v5.0) Toxicity	**Action**
Bradycardia [a] Symptomatic, CTCAE Grade ≥ 2	Consider holding Etcamah dosing whilst evaluating concomitant medicinal products known to cause bradycardia. If no contributing concomitant medicinal product is identified, withhold Etcamah until bradycardia symptoms resolve. If a contributing concomitant medicinal product is identified, consider discontinuing or modifying the dose of this agent until bradycardia symptoms resolve and then restart Etcamah dosing. Consider reassessing the heart rate after restart of Etcamah dosing at next clinical visit or as clinically indicated. Permanently discontinue Etcamah for persistent symptomatic bradycardia.
Visual effects [b] CTCAE Grade ≥ 2/limiting instrumental ADLs	Consider referring to an eye care professional, if visual symptoms are progressive, persistent, or interfere with instrumental ADLs. Decision regarding treatment interruption should be based on clinical assessment.

NCI CTCAE (v5.0) Toxicity	Action
Grade 3 or higher adverse event assessed as causally related to Etcamah	Hold Etcamah dosing until resolution to CTCAE Grade 2 or below, then restart Etcamah dosing. Consider permanently discontinuing Etcamah for recurrent Grade 3 or higher AEs.

ADL = Activities of daily living; AE = Adverse Event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
a. Bradycardia includes bradycardia and sinus bradycardia.
b. Visual effects include photopsia, vision blurred, visual impairment, diplopia, and photophobia of eye disorders MedDRA SOC, and visual perseveration of nervous system disorders MedDRA SOC.

No clinically relevant pharmacokinetic interaction was observed when camizestrant was co-administered with abemaciclib or palbociclib. When camizestrant 75 mg was administered in combination with ribociclib, camizestrant exposure increased to levels comparable to those observed with a 150 mg monotherapy dose (see section 4.9).

Special populations

Elderly
No dose adjustment of camizestrant is required for elderly patients (see section 5.2).

Renal impairment
No dose adjustment of camizestrant is required for patients with mild or moderate renal impairment. Etcamah is not recommended for patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment of camizestrant is required for patients with mild (NCI criteria) hepatic impairment. As a precautionary measure, the use of camizestrant in patients with moderate and severe hepatic impairment should be avoided. Patients with mild hepatic impairment are allowed to take camizestrant (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of camizestrant in children aged 0-18 years has not been established. No data are available.

Method of administration

Oral use.

The tablet should be swallowed whole with water and may be taken with or without food, at approximately the same time each day. Etcamah should not be ingested if it is broken, cracked, or otherwise not intact. The tablet should not be chewed, crushed, dissolved, or divided because these methods have not been studied in clinical studies.

4.3 Contraindications

Breast-feeding (see section 4.6).

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

4.4 Special warnings and precautions for use

Bradycardia, when combined with medicinal products known to increase the risk of QTc prolongation

Bradycardia and QTc prolongation have been reported with camizestrant and CDK4/6 inhibitor combination treatment (see section 4.8). A non-fatal Torsades de Pointes was observed in a patient with bradycardia and QTc prolongation for camizestrant in combination with ribociclib. Considering bradycardia in the context of potential QTc prolongation may increase the risk of arrhythmia, caution should be exercised when administering camizestrant in combination with agents known to cause QTc prolongation, e.g. ribociclib. Refer to monitoring recommendations (see section 4.2).

Hepatic impairment

Camizestrant is metabolised by the liver. Patients with impaired hepatic function are expected to have increased exposure to camizestrant. As a precautionary measure, the use of camizestrant in patients with moderate and severe hepatic impairment should be avoided. Patients with mild hepatic impairment are allowed to take camizestrant. No dose adjustment of camizestrant is required for patients with mild (NCI criteria) hepatic impairment (see sections 4.2 and 5.2).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Camizestrant is a reversible inhibitor of CYP3A4/5 and CYP2B6 and cause inhibition of drug transporters P-gp, BCRP and OATP1B1. Camizestrant is a potent, time-dependent, irreversible inhibitor of CYP2C9 and CYP2C19. Camizestrant is a substrate for CYP3A4/5 and P-gp.

Effects of other medicinal products on camizestrant

CYP3A4/5 inducers
The exposure to camizestrant is expected to decrease if co-administered with moderate and strong CYP3A4/5 inducers. Clinically, a single 75 mg camizestrant dose co-administered orally with repeat doses of carbamazepine, a strong CYP3A4/5 inducer, resulted in camizestrant geometric mean ratios for C_{max} and AUC of 0.41 [90% CI: 0.37,0.46] and 0.29 [90% CI: 0.28,0.32], respectively. The co-administration of camizestrant and a strong CYP3A4/5 inducer (including but not limited to: carbamazepine, phenytoin, rifampicin and St John's Wort) should be avoided. An alternative medicinal product with no or weak potential to induce CYP3A4/5 should be considered.

When co-administering camizestrant in combination with ribociclib, plus a moderate CYP3A4/5 inducer (including but not limited to: e.g. bosentan, nafcillin, modafinil and phenobarbital), no dose adjustment of camizestrant is necessary. When co-administering camizestrant in combination with abemaciclib or palbociclib, the use of such moderate CYP3A4/5 inducers should be avoided by switching to an alternate concomitant drug product (see section 5.2).

CYP3A4/5 inhibitors
In a clinical study, concomitant use of itraconazole, a strong CYP3A4/5 inhibitor, increased camizestrant geometric mean C_{max} and AUC_{inf} by 1.37-fold and 1.90-fold, respectively. Camizestrant in combination with ribociclib should be avoided in patients taking strong CYP3A4/5 inhibitors. In addition, caution should be exercised when combining camizestrant and ribociclib in combination with weak (e.g., chlorzoxazone and fosaprepitant) and moderate (e.g., aprepitant and diltiazem) CYP3A4/5 inhibitors.

Effects of camizestrant on other medicinal products

CYP2C9 and CYP2C19 substrates
In vitro data in conjunction with mechanistic static modelling show that camizestrant is a potent irreversible, time-dependent inhibitor of both CYP2C9 and CYP2C19. This means that the inhibition is irreversible and in order to reinstate functionality, the enzymes need to be synthesised again. Therefore, camizestrant is expected to increase the exposure levels of medicinal products that are substrates of CYP2C9 and/or CYP2C19. No *in vivo* clinical data is available. Medicinal products that are sensitive substrates (including but not limited to: clobazam, omeprazole, pantoprazole and proguanil) or substrates with narrow therapeutic index of CYP2C9 and/or CYP2C19 (including but not limited to: phenytoin and warfarin) should be stopped at least 2 weeks before the first dose of Etcamah and not used for at least 2 weeks after the last dose of Etcamah.

The co-administration of camizestrant and moderately sensitive substrates of CYP2C9 (including but not limited to: flurbiprofen, siponimod and glyburide) and/or CYP2C19 (including but not limited to: esomeprazole, voriconazole and lansoprazole) may be allowed with caution; however, alternative medicinal products should be considered if possible.

CYP3A4/5 substrates
In a clinical study, concomitant use of camizestrant increased midazolam, a sensitive CYP3A4/5 substrate, geometric mean C_{max} by 1.50-fold and AUC by 1.99-fold respectively, therefore, camizestrant is a weak inhibitor of CYP3A4/5. Camizestrant should be used with caution when co-administered with sensitive CYP3A4/5 substrates (including but not limited to: budesonide, buspirone, dronedarone, ivabradine, lurasidone, midazolam, quetiapine, sildenafil and simvastatin). Narrow therapeutic index CYP3A4/5 substrates (e.g. alfentanil and fentanyl) may require dose adjustment and should be monitored closely.

OATP1B1 sensitive substrates
In vitro data show that camizestrant is an inhibitor of OATP1B1. Therefore, camizestrant may increase the exposure levels of medicinal products that are substrates of OATP1B1 including but not limited to glyburide, and lovastatin. No *in vivo* clinical data is available. Medicinal products which have a narrow therapeutic index and are sensitive substrates of OATP1B1 should be avoided. Those medicinal products which are sensitive substrates of OATP1B1 are permitted but caution should be exercised and patients monitored closely for possible drug interactions.

BCRP sensitive substrates
In vitro data show that camizestrant is an inhibitor of Breast Cancer Resistance Protein (BCRP). Therefore, camizestrant may increase the exposure levels of medicinal products that are substrates of BCRP. No *in vivo* clinical data is available. Those medicinal products that are sensitive substrates of BCRP e.g. rosuvastatin, sulfasalazine and sofosbuvir, are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Medicinal products that have a narrow therapeutic index and are sensitive substrates of BCRP should be avoided.

P-gp sensitive substrates
In vitro data show that camizestrant is an inhibitor of P-glycoprotein (P-gp). Therefore, camizestrant may increase the exposure levels of medicinal products that are substrates of P-gp including but not limited to: edoxaban, digoxin, fexofenadine and dabigatran etexilate. No *in vivo* clinical data is available. Medicinal products which have a narrow therapeutic index and are sensitive substrates of P-gp should be avoided. Those medicinal products which are sensitive substrates of P-gp are permitted but caution should be exercised and patients monitored closely for possible drug interactions.

CYP2B6 sensitive substrates
In vitro data show that camizestrant is an inhibitor of Cytochrome P450 2B6 (CYP2B6). Therefore, camizestrant may increase the exposure levels of medicinal products that are substrates of CYP2B6. No *in vivo* clinical data are available. Those medicinal products that are sensitive substrates of CYP2B6 including but not limited to: bupropion, nevirapine, ketamine, and cyclophosphamide should

be avoided. All other CYP2B6 substrates are permitted but caution should be exercised and patients monitored closely for possible drug interactions.

Medicinal products known to prolong the QT interval

Camizestrant in combination with ribociclib has been studied clinically, a non-fatal Torsades de Pointes was observed in a patient with bradycardia and QTc prolongation for camizestrant in combination with ribociclib. It is recommended to monitor patients clinically and adjust doses as specified in the approved ribociclib SmPC. Co-administration of other medicinal products known to prolong the QT interval and/or have a known risk of Torsades de Pointes (e.g. ciprofloxacin, levofloxacin, ondansetron, escitalopram, venlafaxine, fluconazole, chloroquine, halofantrine, clarithromycin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, and pimozide) should be avoided. If concomitant use cannot be avoided, monitor ECGs as clinically indicated (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Based on its mechanism of action and preclinical data, camizestrant may cause foetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving camizestrant. A pregnancy test should be performed and verified as negative on women of childbearing potential prior to initiating treatment and re-testing should be considered throughout treatment.

Contraception in males and females

Women of childbearing potential and men with women partners of childbearing potential have to use effective contraception during treatment with camizestrant and for the following periods after completion of treatment with camizestrant: at least 4 weeks for females and 1 week for males.

Pregnancy

There are no data from the use of camizestrant in pregnant women. Studies in animals have shown reproductive toxicity, including embryo lethality and dystocia (see section 5.3). Based on animal data and its mechanism of action, camizestrant should not be used during pregnancy unless the clinical condition of the women requires treatment with camizestrant.

Breast-feeding

It is not known whether camizestrant and its metabolites are excreted in human milk. Based on animal data (see section 5.3), a risk to the breast-fed child cannot be excluded. Breast-feeding must be discontinued prior to treatment with camizestrant and must not be resumed until 4 weeks following the last dose (see section 4.3).

Fertility

There are no data on the effect of camizestrant on human fertility. Results from animal studies have shown that camizestrant has marked effects on male and female reproductive organs in mice, rats and dogs and functional effects on female and male fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Etcamah in combination with a CDK4/6 inhibitor, has a minor influence on the ability to drive and use machines as the combination may cause fatigue and dizziness (see section 4.8). Etcamah, may cause transient visual effects in the peripheral vision consisting mainly of photopsia, which has no or

negligible influence on the ability to drive. However, patients who experience these symptoms should be advised to observe caution when driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The summary of the safety profile of Etcamah is based on pooled data from 263 patients who received Etcamah in combination with a CDK4/6 inhibitor in phase III (SERENA-6) and phase I (SERENA-1) studies.

The most common adverse reactions (≥ 15%) for Etcamah in combination with a CDK4/6 inhibitor were neutropenia (59.7%), visual effects (40.7%), infections (38.4%), diarrhoea (21.3%), nausea (21.3%), anaemia (21.3%), fatigue (20.5%) bradycardia (19.8%) and leukopenia (15.6%). Among these, ADRs identified for Etcamah were visual effects (40.7%) and bradycardia (19.8%).

The common Grade 3 or 4 adverse reactions (≥ 2%) for Etcamah in combination with a CDK4/6 inhibitor were neutropenia (46.4%), leukopenia (9.1%), anaemia (3.4%), infections (3.4%) and alanine aminotransferase increase (2.3%).

The common serious adverse reactions (≥ 1%) reported in patients receiving Etcamah in combination with a CDK4/6 inhibitor included infections (3.4%) and pyrexia (1.1%).

Adverse reactions leading to treatment discontinuation of Etcamah in patients receiving Etcamah in combination with a CDK4/6 inhibitor were neutropenia (0.4%) and electrocardiogram QT prolonged (0.4%).

The most common adverse reactions (≥ 2%) leading to dose modification of Etcamah in patients receiving Etcamah in combination with a CDK4/6 inhibitor were infections (6.8%), neutropenia (6.5%), bradycardia (4.2%), electrocardiogram QT prolonged (3.4%), diarrhoea (2.3%), vomiting (2.3%) and visual effects (2.3%).

Tabulated list of adverse reactions

Adverse drug reactions identified for Etcamah in the Etcamah and CDK4/6 inhibitors combination are visual effects and bradycardia. Also included in Table 2 are adverse reactions, and their respective incidence, identified for the Etcamah and CDK4/6 inhibitors combination in the Etcamah in combination with a CDK4/6 inhibitor pool (n = 263).

In SERENA-6, the median duration of exposure to Etcamah in combination with a CDK4/6 inhibitor was 15.54 months and to AI in combination with a CDK4/6 inhibitor was 7.36 months.

The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have causes other than the drug, such as the disease, other medication or unrelated causes.

Adverse reactions are listed by MedDRA System Organ Class (SOC) and by descending frequency of the MedDRA grouped term. Frequencies are defined as: 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) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 Adverse drug reactions reported in the Etcamah and CDK4/6 inhibitor combination (n = 263) [a]

MedDRA SOC	MedDRA Term	All Grades category	Grade 3 or 4 category
Infections and infestations	Infections[d,e,f,g]	Very common	Common
Blood and lymphatic system disorders	Neutropenia [e,f,g,h]	Very common	Very common
	Anaemia[e,f,g,i]	Very common	Common
	Leukopenia[e,f,g,j]	Very common	Common
	Thrombocytopenia[e,f,g,k]	Very common	Common
	Lymphopenia[f,g]	Common	Uncommon
	Febrile neutropenia[e,f,g]	Uncommon	Uncommon
Metabolism and nutrition disorders	Decreased appetite[e,f,g]	Common	Uncommon
	Hypokalaemia[g]	Common	Common
	Hypophosphatemia[g]	Common	Uncommon
	Hypocalcaemia[g]	Common	Uncommon
Nervous system disorders	Dizziness[f,g]	Very common	Uncommon
	Headache[f,g]	Very common	Uncommon
	Dysgeusia[e,f]	Common	Uncommon
	Syncope[g]	Common	Uncommon
Eye disorders	Visual effects[b]	Very common	Uncommon
	Dry eye[e,g]	Very common	-
Cardiac disorders	Bradycardia[c]	Very common	-
	Torsades de Pointes[g]	Uncommon	Uncommon
Vascular disorders	Deep vein thrombosis[e,f]	Common	Uncommon
	Embolism[e]	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough[g]	Very common	-
	Dyspnoea[g]	Common	Uncommon
	Pulmonary embolism[e,f]	Uncommon	Uncommon
Gastrointestinal disorders	Diarrhoea[e,f,g]	Very common	Common
	Nausea[e,f,g]	Very common	Uncommon

	Vomiting[e,f,g]	Very common	Uncommon
	Constipation[g]	Common	-
	Abdominal pain[g]	Common	Common
	Stomatitis[e,f,g]	Common	-
Skin and subcutaneous tissue disorders	Pruritus[f,g]	Common	-
	Alopecia[e,f,g]	Common	-
Musculoskeletal and connective tissue disorders	Back pain[g]	Very common	Common
General disorders and administration site conditions	Fatigue[e,f,g]	Very common	Common
	Asthenia[e,g]	Very common	Uncommon
	Pyrexia[e,f,g]	Common	Uncommon
Investigations	Aspartate aminotransferase increased [e,f,g]	Common	Uncommon
	Alanine aminotransferase increased[e,f,g]	Common	Common
	Blood creatinine increased[e,g]	Common	-
	Electrocardiogram QT prolonged[l]	Common	Common

a. Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
b. Visual effects include photopsia, vision blurred, visual impairment, diplopia, and photophobia of eye disorders MedDRA SOC, and visual perseveration of nervous system disorders MedDRA SOC. In addition to camizestrant, vision blurred is an ADR for palbociclib and photopsia is an ADR for abemaciclib.
c. Bradycardia includes bradycardia and sinus bradycardia.
d. All PTs under the Infections and Infestation SOC.
e. ADR for camizestrant and palbociclib combination.
f. ADR for camizestrant and abemaciclib combination.
g. ADR for camizestrant and ribociclib combination.
h. Neutropenia includes neutropenia and neutrophil count decreased.
i. Anaemia includes anaemia, anaemia macrocytic and iron deficiency anaemia.
j. Leukopenia includes leukopenia and white blood cell count decreased.
k. Thrombocytopenia includes thrombocytopenia and platelet count decreased.

Description of selected adverse reaction

Bradycardia
Among the 19.8% patients with bradycardia reported, 85% patients had bradycardia reported as asymptomatic CTCAE Grade 1, while the remaining 15% had Grade 2 adverse reactions reported. Bradycardia exhibited a time-dependent onset where a gradual decrease in heart rate can reach a stable

nadir at approximately 14 days and generally recovered following treatment cessation in a similar time course.

Bradycardia in the presence of drug-induced QTc prolongation has the potential to increase the risk of arrhythmia. QTc prolongation has been reported as an adverse reaction in 18 patients (6.8%) within the Etcamah and CDK4/6 inhibitor combination (see Table 2). Of those, 14 were reported as Grade 1 or Grade 2; 3 were reported as Grade 3 and a Torsades de Pointes (Grade 4) was observed in a patient with bradycardia and QTc prolongation for camizestrant in combination with ribociclib in a phase 1 study. The Grade 3 and 4 events were in combination with ribociclib. Additional monitoring is recommended (see sections 4.2 and 4.4).

Visual effects
Of the 40.7% patients who reported visual effects, the majority (92.5%) experienced CTCAE Grade 1 adverse reactions, while 6.5% patients experienced CTCAE Grade 2 adverse reactions and 0.9% CTCAE Grade 3 adverse reaction (photopsia) occurred. The most common visual effect was photopsia (24.0%). The median time to the onset of the first visual effect was 9 days. Visual effects ADRs were typically intermittent, of brief duration, and not continuous throughout the day. Visual effects were reported not to worsen over time in patients. Ophthalmological review of patients reporting visual effects showed no evidence of structural effects on the eye or clinically meaningful changes in visual acuity attributed to Etcamah (see section 5.1).

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

There is no specific treatment in the event of Etcamah overdose. No Maximum Tolerated Dose (MTD) was reached in the phase I studies in which patients received a daily monotherapy dose up to 450 mg. The safety profile of patients treated with once daily doses of 150 mg Etcamah was consistent with the established safety profile of Etcamah at the recommended 75 mg once daily dose (see section 4.8). In case of suspected overdose, patients should be closely monitored and treated symptomatically, if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Anti-estrogens, ATC code: L02BA05

Mechanism of action

Camizestrant is an oral selective oestrogen receptor degrader (SERD) and oestrogen receptor (ER) antagonist.

Camizestrant binds to the ligand binding domain of ERα, antagonising the activity of ERα encoded by both wild-type *ESR1* and mutated *ESR1*, and inducing proteasome-dependent degradation of ERα, without agonising ERα.

Cardiac electrophysiology
Exposure response analysis of potential QTcI prolongation of daily 75 mg to 300 mg of camizestrant monotherapy was assessed in 30 patients. The predicted drug related mean QTcI prolongation was 2.99 msec (95% CI: (-0.75, 6.73)) at the mean steady state C_{max} with an upper bound of 6.09 msec

(90% CI) following 75 mg camizestrant daily. At the recommended 75 mg dose of camizestrant, a mean increase in QTcI > 10 msec was not observed.

Clinical efficacy

ER-positive, HER2-negative locally advanced or metastatic breast cancer

SERENA-6

SERENA-6 was a randomised, double-blind, circulating tumour DNA (ctDNA)-guided study to assess the efficacy and safety of switching to Etcamah plus a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) versus continuing AI (letrozole or anastrozole) plus a CDK4/6 inhibitor in adult pre/peri/post-menopausal females and males with ER-positive/HER2-negative, locally advanced or metastatic breast cancer with detectable *ESR1*-mutation assessed by ctDNA testing without disease progression during first-line treatment with AI plus a CDK4/6 inhibitor. All patients were required to be currently on treatment and have received ≥ 6 months of AI plus a CDK4/6 inhibitor treatment as the initial endocrine based treatment with no evidence of disease progression as per investigator assessment. Patients could have received one prior line of chemotherapy before the start of AI plus a CDK4/6 inhibitor treatment. Patients with ECOG > 1, presence of widespread symptomatic metastatic visceral disease, early progressors on CDK4/6 inhibitor; severe and uncontrolled cardiac comorbidity, severe hepatic impairment and/or QTc prolongation (defined as > 480 msec for combination with palbociclib or abemaciclib; or ≥ 450 msec for combination with ribociclib were excluded. *ESR1*-mutation status was prospectively determined through testing of plasma-derived circulating tumour DNA (ctDNA) using Guardant 360 CDx assay. Mutations in *ESR1* that cause the indicated amino acids changes were eligible for inclusion E380Q, V422del, S463P, L536H, L536P, L563R, Y537C, Y537D, Y537N, Y537S, D538G. Based on results from the Guardant 360 assay, the most common *ESR1* alterations were variants at amino acids D538G, Y537S, and Y537N detected in 44.6%, 38.9% and 18.5% of patients with an eligible *ESR1*-mutation, respectively.

A total of 315 patients were randomised 1:1 to receive either Etcamah (n = 157, 75 mg once daily) plus a CDK4/6 inhibitor and a placebo of AI or continue AI plus a CDK4/6 inhibitor and placebo of Etcamah (n = 158). The total percentage of randomised patients on palbociclib were 75.6%, ribociclib were 14.9%, and abemaciclib were 9.5%. The choice of CDK4/6 inhibitor and its dose remained the same at the time of randomisation for both arms. Randomisation was stratified by disease site (visceral disease versus non-visceral disease), *ESR1*m detection (first test versus subsequent ctDNA tests), time from initiation of AI plus CDK4/6 inhibitor to randomisation (< 18 months versus ≥ 18 months), and type of CDK4/6 inhibitor (palbociclib versus ribociclib versus abemaciclib). Pre/perimenopausal female patients and male patients taking concomitant LHRH agonist continued to receive it after randomisation. Treatment with Etcamah continued until disease progression or unacceptable toxicity occurred.

The primary endpoint was progression free survival (PFS) as assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The key secondary endpoints were time from randomisation to second progression or death (PFS2) and overall survival (OS).

Demographic and baseline characteristics were well balanced between arms. Of the 315 patients, the median age was 61.0 years (range 29.0 to 89.0 years and 36.8% were over 65 years of age); female (99.0%); male (1.0%); White (63.2%), Asian (23.2%), Black (1.9%), and other races (1.0%). Eastern Cooperative Oncology Group (ECOG) performance status 0 (65.1%) or 1 (33.0%); 79.4% were post-menopausal female and 20.6% were pre-/peri-menopausal female or male.

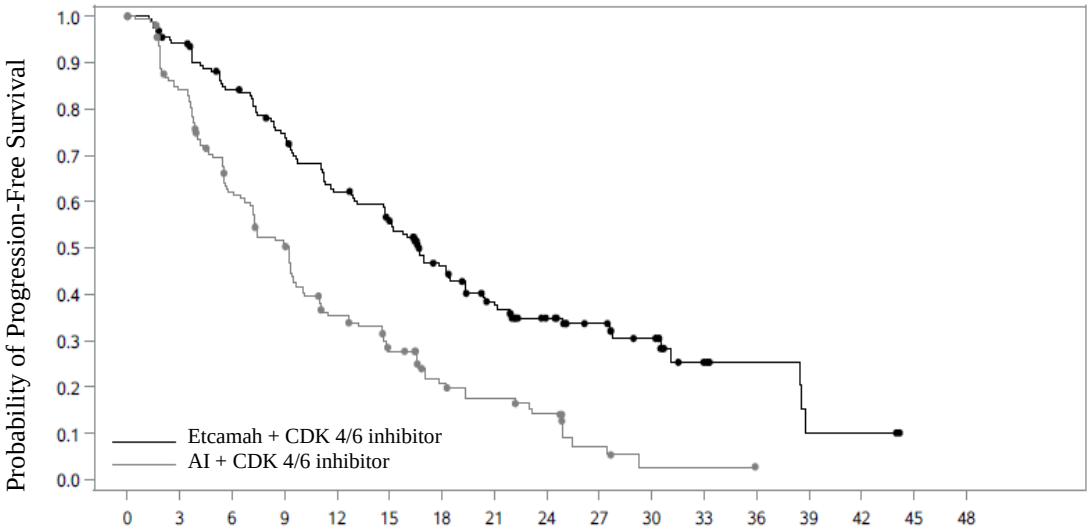
Efficacy results are summarized in Table 3 and Figure 1.

Table 3 Efficacy Results in SERENA-6 (DCO3: 02 Jan 2026)

	Etcamah plus a CDK4/6 inhibitor (n = 157)	**AI plus a CDK4/6 inhibitor (n = 158)**
Progression free survival (PFS) by Investigator assessment		
Number of events [a] (%)	99 (63.1)	124 (78.5)
Median months [b] (95% CI)	16.76 (14.72, 19.35)	9.23 (7.23, 9.66)
Hazard ratio [c] (95% CI)	0.45 (0.34, 0.59)	
p-value [d]	< 0.00001	
Overall survival (OS) (30% maturity)		
Number of events (%)	46 (29.3)	49 (31.0)
Median months [b] (95% CI)	41.20 (35.48, NC)	40.21 (36.50, 43.27)
Hazard ratio [c]	0.87 (0.57, 1.30)	

a. Includes progression events that occur within 2 visits of last evaluable assessment.
b. The calculation is based on the Kaplan-Meier method.
c. A hazard ratio < 1 favours Etcamah plus CDK4/6 inhibitor treatment arm.
d. p value < 0.00001 achieved at DCO1 (28 Nov 2024).

Figure 1 Kaplan-Meier plot of progression-free survival by investigator assessment in SERENA-6



Number of patients at risk

Months	**000**	**003**	**006**	**009**	**012**	**015**	**018**	**021**	**024**	**027**	**030**	**033**	**036**	**039**	**042**	**045**	Number of randomised patients/number of events
Etcamah + CDK 4/6 inhibitor	157	143	125	109	90	78	57	42	31	23	17	7	5	2	2	0	157/99
AI + CDK 4/6 inhibitor	158	127	90	73	48	35	20	16	12	4	1	1	0	0	0	0	158/124

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Etcamah in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Camizestrant pharmacokinetic parameters have been characterized in healthy patients and breast cancer patients. Based on population pharmacokinetic (popPK) analysis, the pharmacokinetics of camizestrant at the 75 mg dose are characterized by an apparent plasma clearance of 69.1 L/h,

apparent volume of distribution (V_{ss}/F) at steady state of 26.97 L/kg and a terminal half-life of approximately 23 hours. The camizestrant 75 mg dose oral bioavailability is 43% and steady state is reached by Day 5 following once daily dosing.

Absorption

Following oral administration, camizestrant is absorbed with median peak plasma concentrations achieved between approximately 2 to 4 hours after dosing.

Effect of food
Similar exposures were observed following administration with a high fat meal or fasted overnight supporting camizestrant being taken with or without food. Following a high fat meal, the fed to fasted C_{max} and AUC geometric mean ratios (90% CI) were 106.2% (90% CI: 94.3%, 119.7%) and 109.8% (90% CI: 104.4%, 115.5%), respectively.

Distribution

Based on popPK analysis, camizestrant is distributed in the tissues with an apparent peripheral volume of distribution of 8.69 L/kg. The apparent volume of distribution of camizestrant at steady state is 26.97 L/kg.

Plasma protein binding of camizestrant is 75.3% (24.7% free). There is no evidence of concentration dependent plasma protein binding. The blood to plasma ratio was 0.99.

Biotransformation

Metabolism results from *in vitro* hepatocytes studies suggest that camizestrant undergoes multiple oxidation reactions in addition to direct N-glucuronidation and is primarily metabolised by CYP3A4/5 and UGT1A4. Human metabolites of camizestrant were detected and quantified in pharmacokinetic samples from healthy female volunteers receiving a single oral dose of 75 mg [14C]-camizestrant (0.67 MBq). The major drug-related circulating materials were the N-glucuronide conjugate of camizestrant, the N-glucuronide of the acid metabolite and camizestrant which accounted for 20.1%, 11.2%, and 13.6% of the circulating radioactivity in plasma. The other eight minor metabolites in plasma, each of which had a relative abundance lower than 10% of the total drug-related materials in plasma, were either oxidative metabolites or glucuronides of oxidative metabolites. No active metabolites have been identified.

In vitro: Camizestrant does not inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19 or CYP2E1 and is a weak (IC50 > 100 μM) inhibitor of UGT1A1 and UGT2B7. Camizestrant does not cause time-dependent inhibition of CYP1A2, CYP2D6 and CYP3A4/5. Camizestrant has low potential to cause induction of CYP1A2, CYP2B6, and CYP3A4/5. For the drug transporters, camizestrant does not inhibit OATP1B3, OCT2, OAT1, OAT3, MATE1, and MATE2K and is not a substrate of BCRP, OATP1B1 or OATP1B3.

Elimination

Following single oral administration of 75 mg [14C]-camizestrant, mean of 82% of the radioactivity administered was recovered in urine and faeces. Mean total radioactivity (65.1%) was recovered in faeces indicating faecal excretion was the main route of elimination following oral dosing; with 16.8% of the total radioactivity being recovered from the urine.

Linearity/non-linearity

Camizestrant AUC and C_{max} showed greater than dose-proportional increase over the dose range of 25 to 450 mg.

Special populations

Effect of age, gender, race and weight
Based on popPK analyses (n = 756), no clinically significant relationships were identified between model predicted steady-state exposure, area under the curve at steady state (AUC_{ss}) and the following covariates: baseline median age 61 years (29 to 89 years) and racial groups. PopPK analysis showed baseline median body weight was 69.9 kg (34.2 to 150 kg) and it affected apparent volume of distribution (V2/F), but this was not clinically relevant; it did not significantly impact apparent total body clearance (CL/F) or AUC_{ss}. No dose adjustments for camizestrant are required based on age, gender, race, or body weight.

Renal impairment
The popPK analysis used continuous creatinine clearance. Baseline creatinine clearance (CrCL) was calculated using the Cockcroft-Gault equation to evaluate the effect of renal function on camizestrant PK; the median CrCL was 86.2 mL/min (range 22.8-303 mL/min). The analysis showed no clinically meaningful impact of mild and moderate renal impairment at baseline on camizestrant PK, indicating that no dose adjustment is necessary for patients with mild to moderate renal impairment.

There were limited patients with severe renal impairment and no patients on dialysis or with CrCL < 15 mL/min were included in the clinical studies of camizestrant. Therefore, an appropriate dose of camizestrant has not been established for severe renal impairment patients and patients on dialysis (see section 4.2).

Hepatic impairment
Based on a pharmacokinetic study in patients following a single 75 mg dose, camizestrant exposure geometric mean C_{max} and $AUC_{0\text{-}INF}$ in patients with moderate (Child-Pugh B) hepatic impairment was 2.4-fold and 2.7-fold, respectively, compared to patients with normal hepatic function. Camizestrant exposure geometric mean C_{max} and $AUC_{0\text{-}INF}$ in patients with severe (Child-Pugh C) hepatic impairment was 3.1-fold and 3.8-fold, respectively, compared to patients with normal hepatic function.

The exposure to camizestrant is higher than dose-proportional and increases with time until steady state. The increase in exposure to camizestrant from single dose to steady state is not known in subjects with hepatic impairment (Child-Pugh). PopPK modelling did not indicate mild hepatic impairment (NCI) as a significant covariate for camizestrant exposure. As precautionary measures, camizestrant should be avoided in subjects with moderate and severe hepatic impairment. Patients with mild hepatic impairment are allowed to take camizestrant.

5.3 Preclinical safety data

Non-clinical/repeat-dose toxicity

In repeat-dose toxicity studies in mice, rats and dogs, the reproductive tract was identified as a target organ with histopathological findings occurring at exposures significantly below (female) or at 2-fold (male) human exposure at Maximum Recommended Human Dose (MRHD). There were related findings in the adrenals (rats and mice) and pituitary (mice) glands. Findings were hormone-driven, based on the pharmacological action of camizestrant and therefore not relevant for post-menopausal women or pre- or peri menopausal women or men administered an LHRH agonist. Findings in the male reproductive tract of clinical relevance are described in the fertility section.

Macrophage aggregation (lung, spleen, thymus and mesenteric lymph nodes) and vacuolation (biliary epithelium of the liver) were noted in the rat and/or mouse. This was confirmed as phospholipidosis in the lung of rat, was reversible following 1-month dosing but was considered adverse in female rats in the 6-month study at a total plasma exposure (AUC) of approximately 60-fold human exposure at MRHD.

In mechanistic studies, camizestrant caused rod bipolar cell dysfunction in the retina of rats at clinically relevant exposures (approximately 5-fold human exposure at MRHD). The retina effects in rats were reversible and are consistent with the transient visual effects observed in humans.

Cardiovascular effects were observed across species (i.e. dogs and rats) and supported by mechanistic studies. Heart rate reduction, related to decreased sinoatrial node pacemaker current activity via HCN4 ion channels, was observed in animals and confirmed clinically (see section 4.4). In dogs and rats, additional delayed-onset cardiovascular functional effects included dose- and time-dependent decreases in diastolic blood pressure, QA interval and PR interval, with increases in pulse pressure, QT/QTc intervals and left ventricular parameters (dP/dt+ and dP/dt-). When assessed in dogs, QTc prolongation persisted for at least 3 days up to 4 weeks. The QTc prolongation was of unknown mechanism, independent of heart rate and unrelated to hERG inhibition and observed at maximum unbound plasma concentrations ≥ 4-fold those at human MRHD. Additional atrial premature complexes (APCs) were observed in one telemetry and one toxicology dog at maximum free plasma levels 12-fold and 33-fold human MRHD, respectively. Cardiomyopathy was observed in female rats following dosing for 6 months at total plasma exposures ≥ 11-fold the human AUC exposure at human MRHD.

In dogs, combination dosing of camizestrant with atropine resulted in a significant increase in plasma and brain exposure of atropine considered to be due to inhibition of atropine metabolism and, therefore, likely dog specific.

Mutagenicity and carcinogenicity

Camizestrant was negative in the *in vitro* Ames and micronucleus assays, and the *in vivo* micronucleus study. Findings in the ovaries in chronic repeat-dose studies included hyperplasia at total plasma exposures (AUC) ≥ 2-fold (rat granulosa cell) and 52-fold (dog sex cord stromal) relative to human exposure at MRHD and benign granulosa cell tumours at total plasma exposures (AUC) of approximately 60-fold (rats) and 3.5-fold (dogs) relative to human exposure at MRHD. An interstitial (Leydig) cell adenoma was observed in the testis of a single dog at 13-fold human exposure at MRHD. Findings are considered hormone-driven, based on the pharmacological action of camizestrant and therefore not relevant for post-menopausal women or in pre- or peri menopausal women or men administered an LHRH agonist.

Reproductive toxicity

Embryofoetal/developmental toxicity
Administration of camizestrant in a modified embryofoetal development study in rats resulted in a complete lack of implantation in females when dosing at 0.1 mg/kg/day commenced prior to implantation. When administration was restricted to the phase of organogenesis, camizestrant had no effect on embryofoetal survival or development, but when dosed from implantation through parturition and into lactation, camizestrant resulted in increased length of gestation, dystocia, impaired offspring survival and growth. Maternal exposures in this study were far below human exposure at MRHD.

Fertility
In a fertility study in female rats, camizestrant negatively affected oestrous cycles, mating behaviour, fertility and early embryonic survival which fully reversed following 1 month off dose. Effects were observed at maternal exposures below human exposure at MRHD.

In male rats and dogs, atrophy of the prostate gland, seminal vesicle and seminiferous tubules, tubular dilation of testis and changes in the epididymis (decreased sperm in rats and cell debris in dog) were evident from the lowest dose in chronic studies at exposures ≥ 2-fold (rat) or ≥ 3.5-fold (dog) human exposure at MRHD and were considered of clinical relevance. In male rats following 9 weeks of dosing there were lower spermatid/sperm counts, a higher percentage of sperm abnormalities, lower sperm motility, and lower mating and pregnancy rates indicating an effect on male fertility. Effects were observed at a total plasma exposure (AUC) ≥ 2-fold that observed at a clinical dose of 75 mg, but a no-effect level was not established. In that study, implantation loss and a decrease in number of live

foetuses was observed in non-dosed females paired with dosed males suggesting male-mediated reproductive toxicity at a total plasma exposure (AUC) 27-fold the human exposure at MRHD. Reversibility of male fertility findings was not assessed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline (type 102)
Calcium hydrogen phosphate
Sodium starch glycolate (Type A)
Magnesium stearate

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

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 storage conditions.

6.5 Nature and contents of container

28x1 film-coated tablets in aluminium/aluminium perforated unit dose blisters. 2 blisters with 14 film-coated tablets each.

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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2046/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due Date**
Post-authorisation efficacy study (PAES): In order to further characterise the long term efficacy of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of *ESR1*-mutation and without disease progression during first-line endocrine therapy in combination with a	31 December 2028

CDK4/6 inhibitor, the MAH shall submit the results of the final OS analysis from the SERENA-6 study, a phase III, randomised, double-blind study.	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

ETCAMAH 75 mg film-coated tablets
camizestrant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 75 mg of camizestrant.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2046/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

etcamah 75 mg

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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ETCAMAH 75 mg tablets
camizestrant

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Etcamah 75 mg film-coated tablets
camizestrant

▼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 or nurse.
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Etcamah is and what it is used for

What Etcamah is

Etcamah contains the active substance camizestrant. Camizestrant belongs to a group of medicines called oral selective oestrogen receptor degrader (SERD) and oestrogen receptor (ER) antagonists.

What Etcamah is used for

Etcamah is a cancer medicine used in adults in combination with another cancer medicine known as a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) to treat breast cancer that has spread nearby (locally advanced) or that has spread to other parts of the body (metastatic). It is important to that you also read the package leaflet for these other medicines. If you have any questions about these medicines, ask your doctor.

Etcamah can only be used when the cancer cells have receptors (targets) on their surface called as oestrogen receptor-positive (ER-positive) and do not have large quantities of a receptor for human epidermal growth factor called HER2 (HER2-negative). The cancer cells must also have been shown to have a change (mutation) in a gene called '*ESR1*' which has been detected while the patient was receiving anti-hormonal therapy together with a CDK4/6 inhibitor as the first treatment for the cancer, while the cancer is not getting worse. Your doctor will also perform a test to make sure that Etcamah is right for you.

When Etcamah is used in women who have not yet reached the menopause (pre-menopausal or perimenopausal) and men, it should be given with a luteinising hormone-releasing hormone (LHRH) agonist or antagonist (medicines that lower blood levels of hormones, such as oestrogen, progesterone and testosterone).

How Etcamah works

The active substance in Etcamah, camizestrant, works by directly blocking and destroying oestrogen receptors found in breast cancer. Oestrogen receptors are proteins that can help the breast cancer grow and multiply. By blocking and destroying the oestrogen receptors found in breast cancer, Etcamah can reduce the growth and spread of the cancer.

2. What you need to know before you take Etcamah

Do not take Etcamah
- if you are breast-feeding.
- if you are allergic to camizestrant or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Etcamah
- if you have reduced heart rate**.**
- if you have any liver-related problems.

Children and adolescents
Do not give this medicine to children or adolescents aged less than 18 years. This is because it is not known how well Etcamah works, or how safe it is in this age group.

Other medicines and Etcamah
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Etcamah can affect the way some other medicines work. Also, some other medicines can affect the way Etcamah works.

- The following medicines can reduce the effectiveness of Etcamah by reducing the amount of Etcamah in the blood:
  - Carbamazepine (used for seizures)
  - St John's Wort (a herbal medicine used for depression)
  - Rifampicin (used to treat certain infections)
- Phenobarbital (used for seizures) and other known moderate CYP3A4/5 inducers may reduce the effectiveness of Etcamah, and they should be used with caution. If possible, your doctor may consider alternative medicines.
- Etcamah can increase the risk of side effects with of some other medicines by increasing the amount of these medicines in the blood. These include:
  - Omeprazole, pantoprazole (used to treat conditions caused by excess stomach acid)
  - Warfarin (used to treat blood clots)
  - Phenytoin (use to treat seizures)

  If you are taking any of these medicines, your doctor will stop the treatment at least 2 weeks before your first dose of Etcamah and will not restart it until at least 2 weeks after your last dose of Etcamah.
- Lansoprazole (used to treat conditions caused by excess stomach acid) and other known moderately sensitive substrates of CYP2C9 and/or CYP2C19 - may be used with caution. If possible, your doctor may consider alternative medicines.
- Medicines known as sensitive CYP3A4/5 substrates for example:
  - Midazolam (used for sleep and/or relieve anxiety) and simvastatin (used to lower cholesterol) - should be used with caution.
  - Alfentanil and fentanyl (medicines used for pain relief) - may require dose adjustments and your doctor may closely monitor their use for possible adverse reactions.
- Taking Etcamah with some medicines may increase the risk of altering your heart rhythm resulting in abnormal electrical activity of the heart (QT prolongation) and Torsades de Pointes (abnormal electrical activity in the heart with life-threatening rhythm disturbance). These include:

- Ciprofloxacin, levofloxacin (used to treat bacterial infection)
- Ondansetron (used to treat nausea and vomiting)
- Escitalopram, venlafaxine (used to treat depression)
- Fluconazole (used to treat fungal infection)
- **Ribociclib** (used for breast cancer in combination with Etcamah)

Ribociclib - Taking Etcamah together with ribociclib has been studied. Your doctor will monitor you during treatment with these medicines and may adjust doses, if necessary. See ribociclib package leaflet for more information.

What you need to know about monitoring with Etcamah and CDK4/6 inhibitors
Before and after you start treatment with Etcamah and a CDK4/6 inhibitor, your doctor will check your heart with an ECG and do blood tests, including checking your blood salts, if required. During treatment, your doctor will continue to monitor you as needed and follow the instructions for the CDK4/6 inhibitor you are taking. If there are changes in your heart rhythm, you may need ECG checks more often.

Pregnancy, breast-feeding and fertility

Birth control (contraception) - information for women and men

Female patients
If you are a woman who can become pregnant, you must use effective birth control while taking Etcamah and for at least 4 weeks after your last dose. Do not use birth control pills. Choose a non-hormonal method like a copper coil. Ask your doctor about suitable methods of contraception.

Male patients
- You must use a condom when having sex with a female partner, even if she is pregnant, while taking Etcamah and for at least 1 week after taking the last dose.
- Your female partner must also use contraception such as the birth control pill.
- You must tell your doctor if your female partner becomes pregnant.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. This is because Etcamah can harm your unborn baby.
- If you do become pregnant during treatment, tell your doctor straight away. Your doctor will decide with you whether you should carry on taking Etcamah.
- Do not become pregnant while taking this medicine. If you are able to become pregnant, you must use effective contraception. See 'Birth control (contraception) – information for women and men' above.
- If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start treatment to check if you are already pregnant. You may also need to do regular pregnancy tests while you are having Etcamah.

Breast-feeding
Before taking Etcamah, tell your doctor, if you are breast-feeding. It is not known whether the medicine passes into breast milk. For the safety of your baby, you must not breastfeed during treatment with Etcamah and for 4 weeks after taking the last dose.

Fertility
Etcamah may decrease fertility in men and women. Talk to your doctor or pharmacist for advice if you are planning to have a baby.

Driving and using machines
Etcamah is taken together with a CDK4/6 inhibitor may cause you to feel tired or dizzy and this can slightly affect your ability to drive or use machines. Etcamah on its own may sometimes cause brief changes in the side of your vision, such as seeing flashes of light. These changes are usually mild and

do not normally affect driving. If this happens, use caution when driving or operating tools or machines.

Etcamah contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

3. How to take Etcamah

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

- Etcamah is available as film-coated tablets which are taken by mouth.
- The recommended dose of Etcamah is one 75 mg film-coated tablet taken once a day at the same time each day.
- Swallow the tablet whole with water. Do not chew, crush, dissolve or divide the tablet.
- Etcamah can be taken with or without food.
- If you vomit, do not take an extra dose. Take the next dose of Etcamah at your usual time.
- Treatment should continue for as long as you benefit from it or the side effects become unmanageable.

If you take more Etcamah than you should
If you take more Etcamah than you should, contact your doctor. Take the tablets and this leaflet with you.

If you forget to take Etcamah
If you forgot to take a dose, you can take it immediately within 6 hours from the time you usually take it. If it is more than 6 hours from the time you usually take your dose, then skip that dose and take the next dose of Etcamah at the usual time. Do not take a double dose to make up for forgotten individual doses.

If you stop taking Etcamah
Do not stop taking Etcamah unless your doctor tells you to.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you get any side effects, including those not listed in this leaflet.

Tell your doctor immediately if you get any of the following symptoms during the treatment:
Fever, sweating or chills, cough, flu-like symptoms, weight loss, shortness of breath, abdominal pain and diarrhoea, warm or painful areas on your body, or feeling very tired (signs or symptoms of infections) (very common, may affect more than 1 in 10 people).

Other side effects:

Very common: may affect more than 1 in 10 people

- Low levels of neutrophils, a type of white blood cell (neutropenia)
- Low levels of white blood cell (leucopenia)
- Low levels of platelets, a componenent that helps the blood to clot (thrombocytopenia)
- Low level of red blood cells (anaemia)
- Dizziness

- Headache
- Visual effects
- Dry eye
- Slow heart rate (bradycardia)
- Cough
- Diarrhoea
- Feeling sick (nausea)
- Vomiting
- Back pain
- Tiredness (fatigue)
- Weakness (asthenia)

Common: may affect up to 1 in 10 people
- Low levels of lymphocytes, a type of white blood cell (lymphopenia)
- Loss of appetite
- Reduced level of potassium in the blood, which could lead to disturbance in heart rhythm (hypokalaemia)
- Reduced level of phosphate in the blood (hypophosphatemia)
- Reduced level of calcium in the blood, which may sometimes lead to cramps (hypocalcaemia)
- Strange taste in the mouth (dysgeusia)
- Fainting (syncope)
- Blood clot in a deep vein, usually in the leg (deep vein thrombosis)
- Shortness of breath or difficulty breathing (dyspnoea)
- Constipation
- Abdominal (belly) pain
- Mouth sores or ulcers with gum inflammation (stomatitis)
- Itching (pruritus)
- Hair loss (alopecia)
- Increased levels of liver enzymes which can be a sign of liver problems
- High blood levels of creatinine, a breakdown product of muscle, which can be a sign of kidney problems
- Abnormal electrical activity of the heart that affects its rhythm (QTc prolongation)

Uncommon: may affect up to 1 in 100 people
- Low levels of white blood cells with fever due to infection (febrile neutropenia)
- Severe irregular heartbeat (Torsades de Pointes) that can cause dizziness, fainting, or collapse
- Obstruction of a blood vessel by a clot (embolism)
- Clot in a blood vessel in the lungs which can cause chest pain, breathlessness and fainting (pulmonary embolism)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Etcamah

Keep out of the reach and sight of children.

This medicine does not require any special storage conditions.

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

Do not use Etcamah if you notice the package or container show signs of damage or tampering or if the tablets are broken, cracked, or otherwise not intact.

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

6. Contents of the pack and other information

What Etcamah contains

- The active substance is camizestrant. Each film-coated tablet contains 75 mg of camizestrant.
- The other ingredients are:
  Tablet core: Cellulose, microcrystalline (type 102), calcium hydrogen phosphate, sodium starch glycolate (Type A) and magnesium stearate (see section 2 'Etcamah contains sodium').
  Tablet coating: Polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172), iron oxide yellow (E172), and iron oxide black (E172).

What Etcamah looks like and contents of the pack

Etcamah 75 mg film-coated tablets (tablets) are beige, round, bi-convex, film-coated tablet, debossed with 'CM' above '75' on one side and plain on the reverse. Approximate diameter: 9 mm.

Etcamah is supplied in 28x1 film-coated tablets in aluminium/aluminium perforated unit dose blisters (each pack contains 2 blisters with 14 film-coated tablets).

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

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

België/Belgique/Belgien
AstraZeneca S.A./N.V.
Tel: +32 2 370 48 11

България
АстраЗенека България ЕООД
Тел.: +359 24455000

Česká republika
AstraZeneca Czech Republic s.r.o.
Tel: +420 222 807 111

Danmark
AstraZeneca A/S
Tlf.: +45 43 66 64 62

Lietuva
UAB AstraZeneca Lietuva
Tel: +370 5 2660550

Luxembourg/Luxemburg
AstraZeneca S.A./N.V.
Tél/Tel: +32 2 370 48 11

Magyarország
AstraZeneca Kft.
Tel.: +36 1 883 6500

Malta
Associated Drug Co. Ltd
Tel: +356 2277 8000

Deutschland
AstraZeneca GmbH
Tel: +49 40 809034100

Eesti
AstraZeneca
Tel: +372 6549 600

Ελλάδα
AstraZeneca A.E.
Τηλ: +30 210 6871500

España
AstraZeneca Farmacéutica Spain, S.A.
Tel: +34 91 301 91 00

France
AstraZeneca
Tél: +33 1 41 29 40 00

Hrvatska
AstraZeneca d.o.o.
Tel: +385 1 4628 000

Ireland
AstraZeneca Pharmaceuticals (Ireland) DAC
Tel: +353 1609 7100

Ísland
Vistor
Sími: +354 535 7000

Italia
AstraZeneca S.p.A.
Tel: +39 02 00704500

Κύπρος
Αλέκτωρ Φαρμακευτική Λτδ
Τηλ: +357 22490305

Latvija
SIA AstraZeneca Latvija
Tel: +371 67377100

Nederland
AstraZeneca BV
Tel: +31 85 808 9900

Norge
AstraZeneca AS
Tlf: +47 21 00 64 00

Österreich
AstraZeneca Österreich GmbH
Tel: +43 1 711 31 0

Polska
AstraZeneca Pharma Poland Sp. z o.o.
Tel.: +48 22 245 73 00

Portugal
AstraZeneca Produtos Farmacêuticos, Lda.
Tel: +351 21 434 61 00

România
AstraZeneca Pharma SRL
Tel: +40 21 317 60 41

Slovenija
AstraZeneca UK Limited
Tel: +386 1 51 35 600

Slovenská republika
AstraZeneca AB, o.z.
Tel: +421 2 5737 7777

Suomi/Finland
AstraZeneca Oy
Puh/Tel: +358 10 23 010

Sverige
AstraZeneca AB
Tel: +46 8 553 26 000

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu