European Union Risk Management Plan	
Drug Substance	Camizestrant
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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR ETCAMAH™ (CAMIZESTRANT)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Applicant's EU Qualified Person for Pharmacovigilance (QPPV).

ETCAMAH™ is a trademark of the AstraZeneca group of companies.

ADMINISTRATIVE INFORMATION

Rationale for submitting an updated RMP

Not applicable for an initial marketing authorisation submission.

Summary of significant changes in this RMP

Not applicable – this is Version 1 of the RMP.

Other RMP versions under evaluation

Not applicable – this is Version 1 of the RMP.

Details of currently approved RMP

Not applicable – this is Version 1 of the RMP.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
ALT	alanine aminotransferase
APC	atrial premature complex
AST	aspartate aminotransferase
bpm	beats per minute
CDK4/6(i)	cyclin-dependent kinase 4/6 (inhibitor)
COPD	chronic obstructive pulmonary disease
eGFR	estimated glomerular filtration rate
EEA	European Economic Area
ER	oestrogen receptor
ERG	electroretinography
ESR1(m)	oestrogen receptor 1 (mutation)
EU-27	27 member countries of the European Union
HER2	human epidermal growth factor 2
hERG	human ether-à-go-go-related gene
HCN	hyperpolarization-activated cyclic nucleotide-gated
HR	hormone receptor
ILD	interstitial lung disease
LH	luteinising hormone
LHRH	luteinising hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NIH	National Institutes of Health
PI	prescribing information
PK	pharmacokinetics
PL	Package Leaflet
QD	once daily
QTca	corrected QT interval
RMP	Risk Management Plan
SERD	selective oestrogen receptor degrader
SEER	Surveillance, Epidemiology and End Results

Abbreviation/ Special term	Definition/Explanation
SERM	selective oestrogen receptor modulator
SmPC	Summary of Product Characteristics
SOC	System Organ Class (per MedDRA)
ULN	upper limit of normal
US	United States

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Camizestrant
Pharmacotherapeutic group(s) (ATC Code)	L02BA05
Marketing Authorisation Applicant	AstraZeneca AB, 15185 Södertälje, Sweden
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	ETCAMAH
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: ETCAMAH is an oral selective ER degrader and complete ER antagonist.
	Summary of mode of action: ETCAMAH 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.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Summary of Product Characteristics
Indication(s) in the EEA	ETCAMAH in combination with a CDK4/6i (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*m and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor.
Dosage in the EEA	The recommended dose of ETCAMAH in combination with a CDK4/6i is 75 mg once daily. Treatment with ETCAMAH should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs. The CDK4/6i should be continued at the same dose at the time of initiation with ETCAMAH as when the *ESR1*m was detected. In pre- or peri-menopausal women and in men, ETCAMAH plus a CDK4/6i should be combined with a LHRH agonist or antagonist.
Pharmaceutical form(s) and strengths in the EEA	Film-coated tablet for oral administration. Each tablet contains 75 mg of camizestrant plus excipients. ETCAMAH 75 mg tablets are beige, round, bi-convex, and debossed with 'CM' above '75' on one side and plain on the reverse.
Is/will the product be subject to additional monitoring in the EU?	Yes

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II.1.1 Breast Cancer

Incidence

Breast cancer is the most common cancer in women, accounting for 2.3 million new cases worldwide in 2022 (IARC 2024a). Approximately 11.6% of all new cancers are female breast cancer, which had a worldwide annual age-standardised (worldwide) incidence rate of 46.8 per 100,000 in 2022 (Bray et al 2024, IARC 2024b). In men, breast cancer is rare, with male breast cancers accounting for less than 1% of all diagnosed cases (Siegel et al 2021, Miao et al 2011).

In the EU-27, 374,800 new cases of female breast cancer were diagnosed in 2023, comprising approximately 29.4% of all cancers in women, with an estimated annual age-standardised (worldwide) incidence rate of 263.6 per 100,000 (ECIS 2023, IARC 2024c). In men, 4,400 new cases of breast cancer were diagnosed in 2022, estimated to account for 0.3% of all diagnosed cancers (ECIS 2023). In the US, it is estimated there will be approximately 310,720 new breast cancer cases in women, and 2,790 new cases in men, diagnosed in 2024 (American Cancer Society 2024).

HR-positive, HER2-negative breast cancer is the most common subtype, accounting for approximately 70% of breast cancer diagnoses (Anderson et al 2002). HR-positive, HER2-negative was the most common subtype of breast cancer in the US, with an age-adjusted rate of 90.0 new cases per 100,000 women based on cases reported between 2017 and 2021 (NCI 2021). In a cohort study based on healthcare administrative data (covering a population of > 10 million patients in Italy in 2013), the crude incidence of HR-positive, HER2-negative metastatic breast cancer was 6.9 per 100,000 women aged ≥ 18 years (Piccinni et al 2019).

Prevalence

Globally, there were approximately 1.9 million women diagnosed with breast cancer in 2022, with 8.2 million women alive who were diagnosed with breast cancer in the previous 5 years (IARC 2024d).

In the EU-27, there were an estimated 1.6 million women living with breast cancer in 2022 who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 688.3 per 100,000 (IARC 2024e).

In the US, there were an estimated 1.1 million women living with breast cancer in 2022 who were diagnosed in the last 5 years, providing a 5-year prevalence proportion of 706.1 per 100,000 (IARC 2024f). For men, the lifetime risk of breast cancer is approximately 1 in 726 (American Cancer Society 2024b).

Approximately 40% of patients at the end of first-line treatment of AI + CDK4/6i have detectable *ESR1*m in ctDNA, and the prevalence of *ESR1*m further rises to > 50% of patients if they have been treated with AI + CDK4/6i for more than one year (Bhave et al 2024, Bidard et al 2022, Chaudhary et al 2024).

Demographics of the population in the authorised indication (age, gender, racial and/or ethnic origin) and risk factors for the disease

Sex*:* Breast cancer is mainly a disease in females, with less than 1% of cases occurring in males worldwide (Siegel et al 2021, Miao et al 2011).

Age*:* Worldwide, 48% of the newly diagnosed breast cancer patients are 45 to 64 years old. In the EU-27 and US, the incidence of breast cancer increases with age, and is most frequently diagnosed in women aged 55 to 75 years. In the US, the median age at the time of breast cancer diagnosis is 62 years, and the highest incidence and prevalence rates are reported among those ≥ 65 years (American Cancer Society 2024c, USCSWG 2022). In men, a study of male breast cancer risk in Denmark, Finland, Geneva, Norway, Singapore, and Sweden indicated the average age at diagnosis was 69.6 years (Miao et al 2011). Similarly, the risk of HR-positive, HER2-negative breast cancer increases significantly with age, with median age at diagnosis of approximately 65 years (Howlader et al 2014, Kulkarni et al 2019, McCarthy et al 2021, Meegdes et al 2023, Piccinni et al 2019).

Race and/or Ethnicity*:* According to SEER data for 2000 to 2021, age-adjusted incidence of breast cancer is highest in White non-Hispanic females and males (177.1 and 1.5 per 100,000 population, respectively) and Black non-Hispanic females and males (121.3 and 1.3 per 100,000 population, respectively) (SEER 2000-2021). Furthermore, in a NIH SEER data registry covering an estimated 28% of the US population in 2010, racial and ethnic differences in HR-positive, HER2-negative breast cancer rates peaked at 75 to 79 years of age, with higher rates for White non-Hispanic patients (342.7 per 100,000), followed by Black non-Hispanic (236.8 per 100,000), Hispanic (190.3 per 100,000), and Asian or Pacific Islander non-Hispanic (176.4 per 100,000) patients (Howlader et al 2014).

Risk factors*:* Risk factors for breast cancer include family history (including hereditary genetic mutations), obesity, radiation exposure, oral contraceptive use, and benign breast disease. Additional risk factors specific to female HR-positive breast cancer include early menarche (before age 12) or late menopause (after age 55), nulliparous women or women who are over age 30 at their first birth, and prolonged post-menopausal hormone therapy use

(Bilimoria and Morrow 1995, McCarthy et al 2021, Kelsey et al 1993, Ronckers et al 2005, CGHFBC 1996, CDC 2023, Shah et al 2005). Additional risk factors specific to male breast cancer include high oestrogen levels, and Klinefelter syndrome (American Cancer Society 2018).

The main existing treatment options

Endocrine-based therapy is the mainstay treatment for HR-positive, HER2-negative breast cancer. Endocrine therapies include AIs, SERMs, and SERDs (ASCO Guidelines 2024, ESMO Guidelines 2023, Gennari et al 2021, NCCN 2024).

Treatment guidelines across many regions have established endocrine therapy (either an AI or a SERD) in combination with a CDK4/6i (palbociclib, ribociclib, or abemaciclib) as the standard-of-care in the first-line for HR-positive, HER2-negative advanced breast cancer in post-menopausal women, premenopausal women (in combination with an LHRH agonist), and men (preferably in combination with an LHRH agonist) (Cardoso et al 2020, Hasset et al 2020, Gennari et al 2021, NCCN 2024).

The optimal subsequent treatment following progression on first-line endocrine therapy plus CDK4/6i remains to be established. Second and later line endocrine-based treatments include endocrine monotherapy, such as fulvestrant, AI, tamoxifen, or elacestrant in patients with a detectable *ESR1*m; endocrine therapy plus targeted therapy include exemestane in combination with everolimus; fulvestrant in combination with alpelisib in patients with *PIK3CA*-mutated tumours, and fulvestrant in combination with capivasertib in patients with tumours harbouring one or more *PIK3CA/AKT1/PTEN*-alterations.

After the exhaustion of endocrine-based therapy, patients eventually require treatment with chemotherapy or antibody-drug conjugates (Moy et al 2022).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Approximately 6% of women diagnosed with breast cancer in the US have metastatic disease at time of diagnosis, and up to 30% of women with early-stage non-metastatic breast cancer will subsequently develop metastatic disease (O'Shaughnessy 2005).

In patients with metastatic breast cancer, bone is the most common site for metastasis (reported in 70.6% of patients) (Savci-Heijink et al 2015). Among patients with breast cancer who had bone metastases, 43.2% developed skeletal-related events, defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopaedic surgery (Jensen et al 2011). Approximately 31% of patients with metastatic breast cancer also experience lung metastasis (Savci-Heijink et al 2015), which typically presents with clinical symptoms of pain, cough, haemoptysis, pleural effusion, and pulmonary

dysfunction, and is associated with poor prognosis (Jin et al 2018). The liver is also a common site for metastasis (reported in 54.5% of patients with breast cancer) and liver metastases represent a frequent cause of mortality among these patients (Savci-Heijink et al 2015). In the majority of cases, liver metastases have been reported as primarily asymptomatic at the time of diagnosis; however, some patients do present with epigastric pain or fullness, palpable hepatomegaly, and/or ascites (Wyld et al 2003).

HR-positive, HER2-negative breast cancer has generally a better prognosis than other subtypes of breast cancer; however, its annual relapse rate continues 10 years after the first diagnosis. In addition, HR-positive breast cancer has a high incidence rate, and for this reason, is the most common cause of breast cancer-related deaths. Although HR-positive breast cancer first responds to endocrine treatment, 15% to 20% of tumours have primary endocrine resistance, and 30% to 40% develop resistance to endocrine treatment during the course of their disease (Lei et al 2019).

Breast cancer is the fourth leading cause of female cancer mortality worldwide, with 666,103 deaths and a 5-year age-adjusted mortality rate of 12.7 per 100,000 (IARC 2024a, IARC 2024g). In Europe, breast cancer mortality was 144,439, with a crude death rate of 37.4 per 100,000 (IARC 2024h). Patients with HR-positive, HER2-negative advanced/metastatic breast cancer typically have a 5-year survival rate of < 30% (Schwartzberg and Greene 2020).

Important comorbidities

Estimates of comorbid conditions that are present at HR-positive, HER2-negative diagnosis suggest that hypertension is the most prevalent comorbidity, with prevalence estimates ranging from 53.3% to 73.9% (Galipeau et al 2019, Zhou et al 2021). Other prevalent comorbidities include dyslipidaemia (66.5%), diabetes (34.6%), COPD (19.8%), stroke (10.6%), coronary heart failure (8.2%), chronic kidney disease (7.9%) and chronic liver disease (0.9%) (Zhou et al 2021).

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of Key Findings From Non-Clinical Data

Key safety findings from non-clinical studies and their relevance to human usage are described below.

Toxicity

- **Key issues identified from acute or repeat-dose toxicity studies:**

  Heart

  ***Cardiovascular Effects*:** Functional cardiovascular effects in dogs were observed at all dose levels in the 14-day, 1-month, and 9-month toxicity studies. Findings included dose dependent decreases in diastolic blood pressure, mean arterial pressure, QA interval, heart rate, and PR interval. Increases in pulse pressure, QT interval, QTca interval, and APCs were also noted after repeat dosing. Findings showed a delayed onset with peak effects occurring at Day 7 to 10 following multiple dosing. Reversibility was demonstrated in the 1-month dog study, where parameters showed recovery to approximate pre-study baseline readings, with the exception of QA interval, which was increased following a 4-week treatment-free phase. Reversibility of the increase in QTca interval was not observed 3 days post-cessation of dosing; however, reversibility was observed by Day 22 of the recovery period.

  A reduction in heart rate in non-clinical species has also been observed in a series of non-clinical mechanistic studies, and in view of the decreased heart rates observed following administration of ETCAMAH, a QT/RR analysis was also performed on the 9-month dog toxicity study. This analysis demonstrated a clear upward shift in the QT/RR relationship, therefore indicating that the QTca prolongation effect observed was not an artefact of the observed bradycardia and was related to ETCAMAH treatment. These non-clinical data indicate that ETCAMAH causes delayed onset QTca prolongation in dogs that is independent of heart rate effects, and is potentially mediated by mechanisms other than direct hERG inhibition.

  The findings in repeat-dose toxicity studies were consistent with those observed in the safety pharmacology rat and dog telemetry studies, in which repeated doses of ETCAMAH had effects on several cardiovascular parameters (most notably arterial pressure parameters, left ventricular parameters, QA interval, heart rate, QTca, and PR intervals). In dogs, peak effects were observed on Days 5 or 7 and subsequently showed evidence of reversibility. APCs were also observed in one of 4 dogs, which showed reversibility. Plasma concentrations were similar throughout the 7 days of dosing, suggesting that the progressive effects on cardiovascular parameters were not the result of a daily accumulation of ETCAMAH in plasma. In rats, non-hERG mediated findings of

heart rate reduction (bradycardia) and QT prolongation (at high single doses) were observed in both single- and repeat-dose telemetry studies.

Relevance to human use: Results from a programme of non-clinical mechanistic studies, in conjunction with data generated from a series of in vitro experiments, are consistent with the hypothesis that ETCAMAH reduces heart rate by decreasing the amount of HCN channel/pacemaker current within the sinoatrial node. These non-clinical findings are therefore considered relevant to human use, and clinical data obtained from the ETCAMAH development programme have confirmed bradycardia as an ADR for ETCAMAH. Bradycardia is therefore listed in Section 4.8 (*Undesirable effects*) of the ETCAMAH SmPC (with additional information provided in SmPC Section 4.4 [*Special warnings and precautions for use*]); however, this event is not considered relevant for inclusion as a safety concern in this EU RMP (see Section II.7.1.1 for details).

It is noted that bradycardia is an independent risk factor for QT prolongation, and bradycardia associated with ETCAMAH dosing in humans can result in an artifactually increased QT interval, under-corrected by the Fridericia correction method. As the mechanism of QTca prolongation in non-clinical studies is unknown, the proarrhythmic risk to humans is unclear. Furthermore, the human relevance of the finding in the rat is unknown due to species differences in ionic mechanisms of repolarisation. However, based on data from ETCAMAH clinical trials to date, there is no evidence that ETCAMAH causes QT prolongation, and the cardiac QTcI study excluded a mean 10 ms increase in QTc interval for ETCAMAH in the 75 mg dose cohort (with the largest mean change from baseline 6.2 ms at 1-hour post-dose). The QTca prolongation findings observed during non-clinical studies are therefore not deemed to be of relevance to human use based on clinical experience.

Furthermore, in the 1-month dog toxicology study, APCs were observed at total plasma levels ≥ 44 times the human clinical exposure at the therapeutic dose of 75 mg QD, and the high APCs incidence in the single telemetered dog were reversible and occurred without any other observable cardiovascular sequelae. Therefore, given the sufficient safety margin and lack of notable sequalae, these findings were not considered to be of relevance to human use.

***Cardiomyopathy*:** Cardiomyopathy was observed in female rats following dosing for 6 months at mid- and high-dose levels. The severity of the finding (mild to moderate) was observed above the threshold of the normal range of background finding of spontaneous chronic progressive cardiomyopathy observed in rats and was therefore considered related to ETCAMAH administration. Heart weight relative to body weight was not increased and there were no histopathological findings in other vasculature examined. Similar effects were not observed in the 9-month dog study.

Relevance to human use: Cardiomyopathy was observed only in a single non-clinical species (rats) at total plasma levels ≥ 11 times the human clinical exposure at the therapeutic dose of 75 mg QD, thereby providing a sufficient safety margin to preclude any meaningful relevance to human use.

Eyes

Repeat-dose toxicology studies have indicated no ophthalmology changes or histology findings in the eye related to ETCAMAH treatment.

Mechanistic ERG studies in rats indicated that ETCAMAH has a functional effect on the retina following observations of dose-dependent decreases in the dark-adapted B-wave and oscillatory potential amplitudes and increases in light adapted B-wave amplitudes and latency times in response to flicker stimuli and increases in amplitudes following sinusoidal stimuli. ETCAMAH treatment led to a marked reduction of the photopic B-wave during the early stages of light adaptation that recovered to control levels by the end of the 10-minute adaptation period. These effects were generally non-progressive, and showed reversal to control levels 7 days after the last ETCAMAH dose.

The data obtained in the rat ERG studies, and the absence of any detectable ocular histopathological changes in toxicity studies, are consistent with the hypothesis that ETCAMAH has a reversible functional pharmacological effect rather than structural effect on the eye.

Relevance to human use: Functional effects on the retina occurred at free plasma levels approximately 5 times the human clinical exposure at the therapeutic dose of 75 mg QD; nevertheless, clinical data obtained from the ETCAMAH development programme have confirmed visual effects as ADRs for ETCAMAH. Visual effects are therefore listed in Section 4.8 (*Undesirable effects*) of the ETCAMAH SmPC; however, these events are not considered relevant for inclusion as a safety concern in this EU RMP (see Section II.7.1.1 for details).

- **Reproductive/developmental toxicity:**

Reproductive-organ toxicity

The principal target organs identified in repeat-dose toxicology studies (≥ 14 days duration) were male and female reproductive tissues in rats, mice, and dogs.

Findings in female reproductive tissues included atrophy of the cervix, uterus, oviduct (rats and mice) and vagina, ovarian cysts, and hypertrophy/hyperplasia of the mammary gland. Hyperplasia (granulosa cell in rat and sex cord stromal in dog) was also observed in the ovaries in the chronic toxicology studies and was considered to be a precursor to benign granulosa cell tumours. Recovery was assessed in the 1-month rat and dog toxicity studies only. Following a 4-week treatment-free period, histopathological findings showed evidence of partial recovery in the ovary, vagina, cervix, uterus, and mammary

gland. Of note, recovery was not assessed in the chronic toxicology studies where hyperplasia and benign granulosa cell tumours were observed.

Findings in male reproductive tissues included tubular degeneration/atrophy in the testis (all species, only at the highest doses tested), hypertrophy/hyperplasia of Leydig cells (mice and dogs only), atrophy in the prostate gland and seminal vesicle (rats only), and atypical residual bodies (mice only). Interstitial cell hypertrophy/hyperplasia was present in the testes of all male dogs, and an interstitial (Leydig) cell adenoma was present in one mid-dose dog (which likely reflected progression of the interstitial cell hypertrophy/hyperplasia).

Relevance to human use: The combination of findings in male and female reproductive tissues are considered secondary to the primary pharmacology of ETCAMAH; however, the development of the single interstitial cell adenoma was observed at total plasma levels ≥ 13 times the human clinical exposure at the therapeutic dose of 75 mg QD, respectively, thereby providing sufficient safety margins to preclude any meaningful relevance to human use.

Furthermore, interstitial (Leydig) cell hypertrophy/hyperplasia and adenoma in the dog are considered to be secondary to alterations in negative feedback loops (leading to increased LH secretion and interstitial cell stimulation) and are not considered relevant for men administered ETCAMAH with an LHRH agonist.

In pre- or peri-menopausal women administered an LHRH agonist, there is suppression of LH production. In post-menopausal women, there is a loss of follicles and associated granulosa cell compartment in the ovary. Therefore, effects that are secondary to hyperstimulation of the gonads by LH are not considered to be relevant for post-menopausal women or for pre- or peri-menopausal women when ETCAMAH is administered with an LHRH agonist.

The impact of these findings in relation to effects on fertility are discussed below.

Fertility

In female rats, ETCAMAH had adverse effects on oestrous cycles and mating behaviour, with a lower rate of fertility. Ovarian and uterine examination revealed effects at all dose levels tested, including lower numbers of corpora lutea, implants, and live embryos, with an associated lower gravid uterus weight. Pre-implantation losses and post-implantation losses were also notably higher than in control animals; however, full reversibility of effects was observed after a 4-week recovery period.

In male rats, there were compound-related histopathology findings in reproductive organs described and changes in sperm count, sperm morphology and reduced sperm motility. Administration of ETCAMAH to male rats also resulted in decreased mating with un-dosed females, and a lower number of live foetuses accompanied by higher implantation loss.

Relevance to human use: Whilst these non-clinical findings indicated the possibility of detrimental effect on reproductive ability, ETCAMAH is only indicated for use in post-menopausal women, or pre-/peri-menopausal women and men who are administered a LHRH agonist, and therefore effects on fertility is not a relevant safety concern for this patient population.

Foetal/development toxicity

In a modified rat embryofoetal development study, administration of ETCAMAH from implantation through organogenesis had no impact on embryofoetal survival, growth or development; however, administration from implantation through gestation resulted in early lactation, gestation length increased, and parturition difficulties, which necessitated the early termination of all females, with and many offspring born deceased. Live litters also had lower survival and low pup weights, and clinical observations noted that maternal females had none/few prominent teats visible.

Relevance to human use: Whilst these non-clinical findings indicated the possibility of foetal/developmental toxicity, ETCAMAH is only indicated for use in post-menopausal women, or pre-/peri-menopausal women and men who are administered a LHRH agonist. Additionally, the SmPC recommends that all patients receiving ETCAMAH should use effective contraception during treatment (and for a defined duration post-treatment discontinuation), and that ETCAMAH should not be used during pregnancy or breastfeeding. This patient population is therefore not deemed to be of childbearing potential, and consequently reproductive/development toxicity does not constitute a safety concern for ETCAMAH.

- **Genotoxicity:**

  ETCAMAH was negative in the in vitro Ames and micronucleus assays, and the in vivo micronucleus study.

  Relevance to human use: Not applicable.

- **Carcinogenicity:**

  A carcinogenicity study is in progress to support the potential clinical development of ETCAMAH in populations other than those referenced in International Council for Harmonisation S9 guidelines; however, these data are not required for the intended breast cancer patient population.

  Relevance to human use: Not applicable.

Safety pharmacology

- **Cardiovascular system, including potential effect on the QT interval**

  The effects of ETCAMAH on the cardiovascular system were evaluated in single and repeat-dose rat telemetry studies, in a repeat-dose dog telemetry study, and as part of dog repeat-dose toxicology studies. These findings have been discussed collectively above.

- **Nervous system**

  No noteworthy effects on neurobehavioral parameters were observed.

  Relevance to human use: Not applicable.

- **Respiratory System**

  No noteworthy effects on respiratory parameters were observed.

  Relevance to human use: Not applicable.

Other toxicity-related information or data

- **Co-administration with atropine**

  Repeat-dose oral administration of ETCAMAH combined with intravenous atropine in dogs was associated with clinical signs (including ataxia, tremors, abnormal gait, limb stiffness, panting, lying on side, agitated, gastrointestinal symptoms and dry mucous membranes) that generally recovered by 3 days post-dose. These clinical observations were considered to be associated with the administration of atropine in the presence of ETCAMAH (and were not observed in the presence of ETCAMAH alone), and PK data have indicated a significant increase in the plasma concentration of atropine when co-administered with ETCAMAH; there was no associated impact on ETCAMAH exposure.

Additional in vitro studies using dog and human liver microsomes were also conducted to further understand the mechanism of the interaction observed in dogs. Findings from these studies indicate that ETCAMAH inhibits the metabolism of atropine to desmethylatropine and hydroxyatropine more potently in dogs than in humans. In addition, quantitation of these metabolites from in vivo studies in dogs indicated that the metabolite levels were higher when dosed alone (atropine-only) versus atropine plus ETCAMAH.

Relevance to human use: The increase in exposure to atropine when co-administered with ETCAMAH is likely dog-specific due to inhibition of atropine metabolism, and inhibition by ETCAMAH is deemed unlikely to cause significant increase in exposure to atropine in humans given that the pathway (N-desmethylation) accounts for only 24% of total elimination routes. Therefore, given the free Cmax in human at 75 mg dose and based on the mechanistic observations, the findings observed in dogs are not considered to be relevant for humans at the therapeutic dose of 75 mg.

- **Phospholipidosis**

  Macrophage aggregation in the lung, spleen, thymus and mesenteric lymph nodes and vacuolation in the biliary epithelium of the liver were noted in rat studies. The macrophage aggregation in the lung was confirmed as phospholipidosis in the 1-month rat study. Findings in the female rat were considered adverse following 6 months dosing due to the increased severity and the association with an inflammatory cell infiltrate (correlating with higher circulating neutrophils, lymphocytes, monocytes and eosinophils). Partial (female) or complete (male) recovery was seen after 28 days off dose. There was no evidence of phospholipidosis in the 1-month or 9-month dog toxicity studies.

  Relevance to human use: The presence of phospholipidosis in the majority of affected tissues in ETCAMAH treated animals was deemed to be an adaptive response and not of toxicological significance due to the absence of tissue damage or functional effects. The presence of macrophage aggregation in the lungs of female rats consistent with phospholipidosis was considered adverse due to severity and the presence of an inflammatory cell infiltrate. Considering the challenge with investigating these events in a clinical setting, the risk to human use is unclear; however, the adverse finding of macrophage aggregation in lungs of female rats occurred at total plasma levels 60 times the human clinical exposure at the therapeutic dose of 75 mg QD, thereby providing sufficient safety margins to preclude any meaningful relevance to human use.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The dataset in support of ETCAMAH for the treatment of ER-positive, HER2-negative locally advanced or metastatic breast cancer was derived from a pooled dataset of 2 clinical studies (Study D8534C00001 [SERENA-6] and Study D8530C00001 [SERENA-1]), in which patients received at least one dose of ETCAMAH 75 mg QD in combination with either palbociclib, abemaciclib or ribociclib (henceforth referred to as the ETCAMAH + CDK4/6i pool).

Exposure to ETCAMAH in the combination ETCAMAH + CDK4/6i pool by months, age group and sex, and race is presented in Table II-1, Table II-2, and Table II-3, respectively.

Table II-1 Duration of Exposure to ETCAMAH (ETCAMAH + CDK4/6i Pool) (N = 263)

Duration of exposure	Number (%) of patients	Patient-years exposure
≥ 0 months	263 (100)	220.9
≥ 1 month	258 (98.1)	220.7
≥ 3 months	214 (81.4)	213.6
≥ 6 months	170 (64.6)	197.1
≥ 12 months	82 (31.2)	131.5
≥ 18 months	39 (14.8)	80.0
≥ 24 months	17 (6.5)	43.9
≥ 30 months	11 (4.2)	31.0
≥ 36 months	3 (1.1)	9.6

Total treatment duration (months) = (min [date of last dose date where dose > 0, date of death, date of DCO] - first dose date + 1)/(365.25/12). A month was counted if at least one dose of ETCAMAH treatment was started in that month, even if full dose was not delivered.

Table II-2 Exposure to ETCAMAH by Age Group and Sex (ETCAMAH + CDK4/6i Pool) (N = 263)

Age group (years)	Male		Female	
	Number (%) of patients	Patient-years exposure	Number (%) of patients	Patient-years exposure
< 45	0 (0)	0	34 (12.9)	23.1
≥ 45 to < 55	0 (0)	0	63 (24.0)	55.1
≥ 55 to < 65	0 (0)	0	72 (27.4)	59.6
≥ 65 to < 75	0 (0)	0	80 (30.4)	68.5
≥ 75	0 (0)	0	14 (5.3)	14.5

Table II-3 Exposure to ETCAMAH by Race (ETCAMAH + CDK4/6i Pool) (N = 263)

Race	Number (%) of patients	Patient-years exposure
White	199 (75.7)	162.0
Asian	38 (14.4)	38.4
Other [a]	12 (4.6)	6.5

[a] Other category includes the following: Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and Other.

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

- ***Paediatric and adolescent patients***
  - Reason for exclusion: This population was excluded from ETCAMAH clinical studies based on the general principle that paediatric patients are not exposed to the investigational product where the benefit-risk profile for the intended adult population has not yet been established.
  - Is it considered to be included as missing information: No
  - Rationale: Breast cancer is a disease of adults, with only exceptional occurrence in the paediatric population (Kennedy and Boughey 2013). Consequently, use in paediatric and adolescent patients is not indicated or anticipated for the target indication, and therefore this population is not relevant for inclusion as missing information.

- ***Patients with an Eastern Cooperative Oncology Group performance status of ≥ 2***
  - Reason for exclusion: Patients with poor performance status are generally excluded from clinical studies to ensure they are well enough to attend the trial site and comply with study procedures, and to ensure the optimal assessment of safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: Given the early-stage disease setting of the target patient population, it is considered unlikely that patients prescribed ETCAMAH would have a performance status of ≥ 2, and there is additionally no pharmacological rationale to suspect that the safety profile of ETCAMAH in patients who do have significant limitations in their daily activities would differ from that of the general indicated population. Consequently, this criterion is not relevant for inclusion as missing information.

- ***Pregnant and/or breastfeeding women***
  - Reason for exclusion: Women who are pregnant or breastfeeding are generally excluded from oncology clinical studies to avoid potential harm to the unborn foetus or breastfed infant.
  - Is it considered to be included as missing information: No
  - Rationale: Section 4.6 (*Pregnancy and lactation*) of the ETCAMAH SmPC recommends that all patients receiving ETCAMAH should use effective forms of contraception during treatment (and for a defined duration post-treatment

discontinuation), and that ETCAMAH should not be used during pregnancy or breastfeeding. Additionally, female patients of childbearing potential should concomitantly receive an LHRH agonist in conjunction with ETCAMAH treatment, and consequently are not expected to become pregnant or to breastfeed. ETCAMAH use in pregnant and/or breastfeeding women is therefore not anticipated, and consequently this patient population is not relevant for inclusion as missing information.

- ***Patients with clinically significant reduced haematological parameters***
  - Reason for exclusion: Patients with clinically significant pre-existing reduced haematological parameters are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Consequently, patients with a baseline haemoglobin of ≥ 8 g/dL and/or an absolute neutrophil count of ≥ 1000/mm^3 were generally excluded from ETCAMAH clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Data from non-clinical studies have not identified any adverse impact on haematological parameters in animals dosed at total plasma levels corresponding to human clinical exposure at the therapeutic dose of 75 mg QD. Additionally, monotherapy data from the ETCAMAH clinical development programme have indicated that ETCAMAH has no detrimental effect on haematological parameters at doses exceeding the indicated posology, and no safety signal has been identified from a review of haematological AEs when ETCAMAH is administered in combination with a CDK4/6i. Consequently, there is no reason to suspect a different safety profile in patients with reduced haematological parameters at baseline, and this patient population is therefore not considered relevant for inclusion as missing information.

- ***Patients with moderate or severe hepatic impairment***
  - Reason for exclusion: Patients with pre-existing hepatic impairment are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Consequently, patients with an ALT and AST of ≤ 3 × ULN (or ≤ 5 × ULN for patients with hepatic metastases), a total bilirubin of ≤ 1.5 × ULN (or ≤ 3 × ULN in the presence of documented Gilbert's syndrome), or an alkaline phosphatase of ≤ 2.5 × ULN (or ≤ 5.0 × ULN if bone or liver metastases present) were excluded from ETCAMAH clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Data from a Phase I, single-dose study, conducted to evaluate the effect of hepatic impairment in relation to the PK, safety, and tolerability of ETCAMAH 75 mg QD, have confirmed that there were no apparent differences in safety profile between patients with normal hepatic function (n = 8 patients) and patients with

moderate (n = 8 patients) or severe (n = 6 patients) hepatic impairment (per Child-Pugh classification) (Study D8532C00002).Nevertheless, population PK modelling of camizestrant 75 mg indicates that impaired hepatic function can result in increased camizestrant exposure, with exposure increasing by hepatic impairment category.

Consequently, as a precautionary measure, Section 4.2 (*Posology and method of administration*) and Section 4.4 (*Special warnings and special precautions for use*) of the SmPC states that the use of ETCAMAH in patients with moderate and severe (per NCI criteria) hepatic impairment should be avoided. Administration of ETCAMAH to patients with moderate and severe hepatic impairment is therefore not anticipated, and consequently, this patient population is not deemed relevant for inclusion as missing information.

- ***Patients with moderate or severe renal impairment***
  - Reason for exclusion: Patients with varying degrees of pre-existing impaired renal function are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Consequently, patients with a serum creatine ≤ 1.5 × ULN, or calculated creatinine clearance ≥ 30 mL/min as determined by Cockcroft-Gault, were excluded from ETCAMAH clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Data from PK studies have indicated that renal clearance is not the major route for unchanged ETCAMAH elimination, and a population PK analysis has suggested that there is no clinically relevant effect on drug exposure associated with baseline mild and moderate renal impairment. There were limited patients with severe renal impairment, and no patients on dialysis or with creatinine clearance < 15 mL/min included in the clinical studies of ETCAMAH.

    Consequently, Section 4.2 (*Posology and method of administration*) of the ETCAMAH SmPC advises that no dose adjustment of ETCAMAH is required for patients with moderate renal impairment, as there is no scientific rationale to suggest that the safety profile of these patients would be different from that of the general indicated population. This patient population is therefore not deemed relevant for inclusion as missing information.

    The SmPC also states that ETCAMAH is not recommended for use in patients with severe renal impairment. Considering this guidance, usage in these patients is not expected, and therefore this population is not considered to be relevant for inclusion as missing information.

- ***Patients with CDK4/6i treatment-induced symptomatic ILD (Grade ≥ 2)***
  - Reason for exclusion: ILD is a recognised risk of palbociclib, abemaciclib, and ribociclib treatment, and therefore patients with a prior treatment-induced symptomatic ILD were excluded from clinical studies in which patients received ETCAMAH in combination with these treatments to ensure the optimal assessment of ETCAMAH safety and efficacy data.
  - Is it considered to be included as missing information: No
  - Rationale: This exclusion criteria was related to the medications co-administered with ETCAMAH in the clinical development programme (all of which have ILD listed as an ADR in their PI), and a review of monotherapy data from the ETCAMAH clinical development programme has not indicated an association between ETCAMAH treatment and ILD. Consequently, there are no exclusions in the SmPC on the use of ETCAMAH in this patient population, and patients with a history of ILD should be managed according to individual CDK4/6i labelling guidance. This patient population is therefore not considered relevant for inclusion as missing information.

- ***Patients with a known or family history of severe structural or ischaemic heart disease***
  - Reason for exclusion: Patients with significant personal or family history of cardiovascular conditions are generally excluded from clinical studies to avoid factors that may confound the understanding and interpretation of safety data. Consequently, patients with a known or family history of myocardial infarction, severe aortic regurgitation, unstable angina pectoris, cerebrovascular accident, transient ischaemic attack, left ventricular ejection fraction < 50%, or a recent procedure to correct structural heart disease, were excluded from ETCAMAH clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Non-clinical and clinical data do not support an association between ETCAMAH and structural or ischaemic cardiotoxicity at the therapeutic dose of 75 mg QD. This absence of cardiac liability suggests that the safety profile in patients with these cardiovascular conditions would not be different from that of the indicated population, and therefore the use of ETCAMAH in these patients is not relevant for inclusion as missing information.

- ***Patients with clinically important abnormalities in cardiac rhythm (including a resting heart rate of < 55 bpm)***
  - Reason for exclusion: A reduction in heart rate in non-clinical species was observed in a series of mechanistic studies. Therefore, in order to protect the safety of patients,

those with a resting heart rate < 55 bpm, unexplained syncope, symptomatic hypotension, second- and third-degree heart block, or clinically significant sinus pause or sinoatrial block, were excluded from ETCAMAH clinical studies.

- Is it considered to be included as missing information: No
- Rationale: Bradycardia is listed as an ADR in Section 4.8 (*Undesirable Effects*) of the ETCAMAH SmPC, with additional information provided in SmPC Section 4.4 (*Special warnings and precautions for use*). Whilst patients with pre-existing clinically important abnormalities in cardiac rhythm could theoretically be at an increased risk of further decreases in heart rate, a review of clinical study data at the indicated posology confirmed that all patients reporting instances of bradycardia remained in sinus rhythm, with the majority of occurrences reported as asymptomatic. Furthermore, epidemiological data indicate that the median age of patients with metastatic breast cancer (ie, the target patient population) is approximately 65 years old, with population-based studies reporting a median heart rate of approximately 80 bpm in this demographic. When taken together, these data indicate that exposure in this patient population is expected to be limited, and adverse clinical consequences as a result of bradycardia are unlikely. Any risk to this patient population is therefore considered to be adequately addressed via routine risk communication in the ETCAMAH SmPC, and this patient population is therefore not considered relevant for inclusion as missing information.

- ***Patients with any factors that increase the risk of QTc prolongation***
  - Reason for exclusion: Prolongation of the QT interval was observed in non-clinical rat and dog studies. Therefore, in order to protect the safety of patients, those with a resting QTcF interval > 480 ms (or ≥ 450 ms in combination with ribociclib), electrolyte abnormalities, or any factors that increase the risk of QTc prolongation (eg, long QT syndrome) were excluded from ETCAMAH clinical studies.
  - Is it considered to be included as missing information: No
  - Rationale: Based on data from ETCAMAH clinical trials, there is no evidence that ETCAMAH causes QT prolongation, and the cardiac QTcI study excluded a mean 10 ms increase in QTc interval for ETCAMAH in the 75 mg dose cohort (with the largest mean change from baseline 6.2 ms at 1-hour post-dose). Consequently, there is no clinical evidence to suggest that the use of ETCAMAH in patients with any factors that increase the risk of QTc prolongation will result in a different safety profile to that of general indicated population and this patient population is therefore not considered relevant for inclusion as missing information.

    Of note, based on the safety profile of ribociclib, Section 4.2 (*Posology and method of administration*) of the ETCAMAH SmPC provides guidance that treatment with

ETCAMAH in combination with ribociclib should be initiated only in patients with QTcF values less than 450 msec, and following electrolyte testing prior to initiating treatment. Accordingly, administration of ETCAMAH in combination with ribociclib to patients with underlying risk factor for QT prolongation is not anticipated, and consequently, this patient population is not deemed relevant for inclusion as missing information.

- ***Patients who had undergone a major surgical procedure or significant traumatic injury within 14 days of starting ETCAMAH treatment, or patients anticipated to require future major surgery and/or any surgery requiring general anaesthesia***
  - Reason for exclusion: The potential for an interaction between ETCAMAH and atropine was identified in non-clinical studies, therefore patients who had recently undergone or require future major surgery (which may entail administration of atropine in an anaesthetic context) were excluded from ETCAMAH clinical studies in order to maintain a positive benefit-risk balance.
  - Is it considered to be included as missing information: No
  - Rationale: Since the start of the ETCAMAH clinical development programme, the non-clinical findings which prompted this exclusion criterion have been further investigated and concluded the effect to be likely dog-specific (see Section II.2.1 for details). Based on this revised assessment, ETCAMAH is deemed unlikely to cause significant increase in exposure to atropine in humans. There is consequently limited scientific rationale to suggest that the co-administration of atropine with ETCAMAH during clinical use will result in a different safety profile to that of general indicated population, and this patient population is therefore not considered relevant for inclusion as missing information.

- ***Use of strong inhibitors/inducers of CYP3A4/5, sensitive CYP2B6 substrates, and drugs which are substrates of CYP2C9 and/or CYP2C19 which have a narrow therapeutic index***
  - Reason for exclusion: ETCAMAH is predominantly metabolised via CYP3A4/5, and therefore the co-administration of compounds which are strong inhibitors or inducers of CYP3A4 may increase or decrease exposure to ETCAMAH, respectively, and may consequently adversely affect the toxicity or efficacy profile of ETCAMAH accordingly. ETCAMAH is also a potent inhibitor of CYP2B6 and a time-dependent inhibitor of CYP2C9 and CYP2C19, therefore the co-administration of compounds that are sensitive substrates of CYP2B6, or substrates of CYP2C9, or CYP2C19 with a narrow therapeutic index may increase their exposure and hence potentially adversely affect toxicity. The concomitant use of such compounds was therefore an exclusion criterion in ETCAMAH clinical

studies to ensure optimal assessment of the efficacy and safety profile of ETCAMAH.

- Is it considered to be included as missing information: No
- Rationale: Based on PK modelling, Section 4.5 (*Interaction with other medicinal products and other forms of interaction*) of the ETCAMAH SmPC states that the concomitant use of strong inhibitors/inducers of CYP3A4/5, sensitive substrates of CYP2B6, and drugs which are sensitive substrates or substrates with a narrow therapeutic index of CYP2C9 and/or CYP2C19, should be avoided. Considering this guidance, usage of these medications is not expected, and therefore these patient populations are not considered to be relevant for inclusion as missing information.

II.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

II.4.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table II-4 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure ETCAMAH + CDK4/6i Pool
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment:	
Moderate hepatic impairment [a]	0 patients [b]
Severe hepatic impairment [a]	0 patients [b]
Patients with renal impairment:	
Moderate renal impairment [c]	62 patients [b]
Severe renal impairment [c]	1 patient [b]
Patients with cardiac impairment (including QTc prolongation, heart failure, uncontrolled hypotension, left ventricular ejection fraction decreased, or cardiac arrhythmia)	Not included in the clinical development programme
Immunocompromised patients	No data available
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Patients with relevant different ethnic origin:	
Asian	38 patients
White	199 patients
Other [d]	12 patients
Subpopulations carrying relevant genetic polymorphisms	No data available

[a] The definitions for hepatic impairment are as follows: moderate hepatic impairment = bilirubin > 1.5 × ULN to ≤ 3 × ULN and any AST; and severe hepatic impairment = bilirubin > 3 × ULN and any AST.

[b] Derived from the number of patients with hepatic and renal impairment from the 2 clinical studies in the ETCAMAH + CDK4/6i Pool (SERENA-1 and SERENA-6) who were included in the population PK modelling analysis (Report MS-2025-01), regardless of ETCAMAH dose received.

[c] The definitions for renal impairment are as follows: moderate renal impairment: eGFR ≥ 30 to < 60 mL/min/1.73 m^2, and severe renal impairment: eGFR ≥ 15 to < 30 mL/min/1.73 m^2.

[d] Other category includes the following options in the CRF: Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and Other.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

Not applicable.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

ETCAMAH is not likely to have a potential for drug abuse and no findings during the clinical study programme indicate that ETCAMAH induces drug abuse. The product will be made available by prescription only.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of Safety Concerns in the Initial RMP Submission

It is noted that the content of this section reflects the assessment at the time of the initial EU RMP (Version 1) and will not be updated.

II.7.1.1 Risk not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The reasons for not including a risk in the list of safety concerns in the initial EU RMP are presented below:

- *Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):*
  - Bradycardia (including sinus bradycardia):
    - Whilst these events have been confirmed as common ADRs for ETCAMAH, cases were exclusively non-serious, mild or moderate in severity, and did not result in treatment discontinuation.
  - Visual effects (including photopsia, vision blurred, visual impairment, diplopia, and photophobia of eye disorders MedDRA SOC, and visual perseveration of nervous system disorders MedDRA SOC):
    - These events have been confirmed as very common ADRs for ETCAMAH; however, visual effects were exclusively non-serious, typically intermittent (ie, not continuous throughout the day) and of brief duration, and did not result in treatment discontinuation or worsen over time.

II.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no topics classified as important risks or missing information for ETCAMAH in the initial EU RMP.

II.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

II.7.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

II.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no important risks for ETCAMAH.

II.7.3.2 Presentation of the Missing Information

There is no missing information for ETCAMAH.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of Safety Concerns

There are no safety concerns for ETCAMAH (Table II-5).

Table II-5 Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Not applicable.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

A summary of the planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or are specific obligations is provided in Table IV-1.

Table IV-1 Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or are Specific Obligations

Study code (name) / Short title Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date for EMA
Efficacy studies which are conditions of the marketing authorisation				
Study D8534C00001 (SERENA-6) A Phase III, double-blind, randomised study to assess switching to camizestrant + CDK4/6i versus continuing AI + CDK4/6i in ER-positive/HER2-negative metastatic breast cancer patients with a detectable *ESR1* mutation without disease progression during first-line treatment. • ***Status:*** Ongoing	To further characterise the long-term efficacy of camizestrant in combination with a CDK4/6i (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	• Overall survival (no detriment)	Final analysis of overall survival	31 Dec 2028
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Not applicable.

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR ETCAMAH (CAMIZESTRANT)

Summary of risk management plan for ETCAMAH (camizestrant)

This is a summary of the risk management plan (RMP) for ETCAMAH. The RMP details important risks of ETCAMAH, and how more information will be obtained about ETCAMAH's risks and uncertainties (missing information).

ETCAMAH's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how ETCAMAH should be used.

This summary of the RMP for ETCAMAH should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the ETCAMAH RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

ETCAMAH is authorised in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for the treatment of adult patients with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (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. It contains camizestrant as the active substance and is given as one oral 75 mg tablet once daily.

Further information about the evaluation of ETCAMAH's benefits can be found in ETCAMAH's EPAR, including in its plain-language summary, available on the EMA website under the medicine's webpage.

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of ETCAMAH, together with measures to minimise such risks and the proposed studies for learning more about the risks of ETCAMAH, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and PL addressed to patients and healthcare professionals

- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

VI.2.1 List of Important Risks and Missing Information

Important risks of ETCAMAH are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ETCAMAH. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	None
Missing Information	None

VI.2.2 Summary of Important Risks

There are no important risks or missing information for ETCAMAH.

VI.2.3 Post-Authorisation Development Plan

VI.2.3.1 Studies Which are Conditions of the Marketing Authorisation

The following study is a condition of the marketing authorisation:

- **Study D8534C00001 (SERENA-6) – A study to assess switching to camizestrant + CDK4/6 inhibitor versus continuing aromatase inhibitors + CDK4/6 inhibitor in ER-positive / HER2-negative metastatic breast cancer patients with a detectable *ESR1* mutation without disease progression during first-line treatment**
  - *Purpose of the study*: To further characterise the long-term efficacy of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, abemaciclib or ribociclib) in adult patients with ER-positive, HER2-negative metastatic breast cancer upon detection of *ESR1* mutation and without disease progression during first line endocrine therapy.

VI.2.3.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for ETCAMAH.

VII. PART VII: ANNEXES

Annex 4 Specific Adverse Drug Reaction Follow-Up Forms *(Not Applicable)*

Annex 6 Details of Proposed Additional Risk Minimisation Activities *(Not Applicable)*

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms (Not Applicable)

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimisation Activities (Not Applicable)

Not applicable.

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