EU Risk Management Plan (Version 2.2)

Global Patient Safety
Signatory information is available on request.

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EU Risk Management Plan for Abemaciclib

RMP version to be assessed as part of the application: 2.2

Data lock point for this RMP: 28 March 2020 (for clinical data); 31 August 2025 (for post-authorisation exposure data)

Date of final sign off: See cover page

Rationale for submitting an updated RMP:

This RMP was updated based on the EMA's Request for Supplementary Information received on 05 January 2026 for the EU RMP Version 2.1 (Procedure Number EMA/VR/0000307389).

Summary of significant changes in this RMP:

Changes are related to

- Parts III.1, V.3, and Annex 4: Pregnancy and Breastfeeding Outcome - Maternal and Paternal follow-up questionnaire was removed.
- Module SV: the post-authorisation exposure data was updated with the latest available numbers.
- Module SI.1.3: a typo error has been corrected.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP

Version number: 1.3

Approved with procedure: EMEA/H/C/004302/II/0013

Date of approval (opinion date): 24 February 2022

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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List of Abbreviations

Term	Definition
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
ALT	alanine aminotransferase
APLD	anonymised patient-level data
AST	aspartate aminotransferase
CDK	cyclin-dependent kinase
CI	confidence interval
CSR	clinical study report
eBC	early breast cancer
ER	oestrogen receptor
ET	endocrine therapy
GI	gastrointestinal
GLP	good laboratory practice
GnRH	gonadotropin-releasing hormone
GVP	good pharmacovigilance practice
HER2	human epidermal growth factor receptor 2
ICH	International Council for Harmonisation
HR	hormone receptor
MAA	marketing authorisation application
mBC	metastatic breast cancer
NCCN	National Comprehensive Cancer Network
PV	pharmacovigilance
RMP	risk management plan
SEER	Surveillance, Epidemiology, and End Results

SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VTE	venous thromboembolic event

Part I: Product Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Abemaciclib (LY2835219)
Pharmacotherapeutic group(s) (ATC Code)	L01XE
Marketing Authorisation Applicant	Eli Lilly and Company
Medicinal product to which this RMP refers	Abemaciclib
Invented name in the European Economic Area (EEA)	VERZENIOS®
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** CDK4 and CDK6 dual inhibitor
	Summary of mode of action: Abemaciclib is an inhibitor of cyclin D-dependent kinases CDK4 and CDK6 and was most active against cyclin D1/CDK4 in enzymatic assays. In breast cancer, cyclin D1/CDK4 has been shown to promote phosphorylation of the retinoblastoma protein (Rb), cell proliferation and tumour growth. Abemaciclib prevents Rb phosphorylation, blocking progression from G1 to S phase of the cell cycle, leading to suppression of tumour growth in preclinical models following short-duration target inhibition. In oestrogen receptor-positive breast cancer cell lines, sustained target inhibition by single-agent abemaciclib prevents rebound of Rb phosphorylation and cell cycle re-entry, resulting in senescence and apoptosis. In vitro, Rb-negative and Rb-depleted cancer cell lines are generally less sensitive to abemaciclib. In vivo, abemaciclib monotherapy dosed daily without interruption at clinically relevant concentrations in breast cancer xenograft models resulted in reduction of tumour size.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	The proposed PI is provided with this submission.
Indication in the EEA	**Current:** Advanced or Metastatic Breast Cancer Verzenios is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2-negative (HER2−), locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with luteinising hormone-releasing (LHRH) agonist.
	Proposed: Early Breast Cancer Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with HR-positive, HER2−, node-positive early breast cancer at high risk of recurrence.

	In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.
Dosage in the EEA	**Current:** *Verzenios in combination with endocrine therapy:* The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Abemaciclib will be supplied as: Immediate-release film-coated tablets: 50, 100 and 150 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; INN = International Non-proprietary Names; PI = package insert; RMP = risk management plan.

Part II: Safety Specification.

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Breast Cancer

Breast cancer is a heterogeneous disease, with 4 major molecular subtypes: hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-), HR+/HER2+, HER2-enriched (HR-/HER2+), and triple negative (HR-/HER2-). The HR+/HER2- subtype is the most common subtype, accounting for approximately 70% of breast cancers (ACS 2019).

The target populations for abemaciclib comprise (a) patients with HR+/HER2- eBC with a high-risk of recurrence and (b) patients with HR+/HER2- advanced or mBC. Each indication is estimated to represent 15% to 30% and approximately 5% of HR+/HER2- breast cancers, respectively (Akinyemiju et al. 2015; Gluz et al. 2016; Auguste et al. 2017).

Most breast cancer statistics include all breast cancers, regardless of molecular subtype or stage at diagnosis. Clinically relevant differences in the target populations distinct from the general epidemiology of overall breast cancer are highlighted as relevant.

SI.1.1 Incidence

Breast cancer is the most common cancer in women in almost all countries (Cardoso et al. 2012). Globally, the incidence rates have increased by 17% between 1990 and 2013, although the temporal increase was more evident in developing countries (46%) than in developed countries (8%) (Fitzmaurice et al. 2015). According to the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, an estimated 2.1 million new cases of female breast cancer were reported in 2018 (Bray et al. 2018). The 2018 age-standardised annual incidence rate of breast cancer among females (per 100,000) globally and across different regions was as follows: 46.3 (world); 34.4 (Asia); 37.9 (Africa); 51.9 (Latin America); 74.4 (Europe); 84.8 (North America); and 86.7 (Oceania) (Bray et al. 2018).

Males are disproportionately less affected by breast cancer, accounting for approximately 1% of all breast cancers. The male/female ratios of incident breast cancer were reported to range from 1/83.9 globally to 1/105.5 in the United States and 1/141 in the United Kingdom (Cancer Research UK; Siegel et al. 2017; Li et al. 2019).

SI.1.2 Prevalence

There were almost 6.88 million women worldwide living with breast cancer in 2018, who were diagnosed within the past 5 years. The estimated 5-year prevalent female breast cancer cases across different regions (in millions) were as follows: 2.62 (Asia); 2.05 (Europe); 1.1 (North America); 0.62 (Latin America); 0.37 (Africa); and 0.10 (Oceania) (Bray et al. 2018).

Direct estimates of prevalent breast cancer cases among males are not available. However, given that male patients with breast cancer have a higher mortality rate across stages compared with

their female counterparts (Wang et al. 2019), the number of prevalent male breast cancer cases is expected to account for 0.6% to 1% of all prevalent breast cancer cases.

SI.1.3 Demographics of the Population in the Proposed Indication [Age, Gender, Racial and/or Ethnic Origin] (when relevant for management) and Risk Factors for the Disease

Age

The median age at diagnosis for breast cancer was 62 years in female patients and 68 years in male patients (SEER CSR Table 11.2). Breast cancer is most frequently diagnosed in women aged 55 to 64 years. The age distribution of new female breast cancer cases in Europe and the United States is presented in Table SI.1.

Table SI.1. Age Distribution (%) of Incident Cases for Female Breast Cancer

Age at Diagnosis, Years	<20	20-34	35-44	45-54	55-64	65-74	75-84	>84
CI-5, 2003-2007	0.0	1.7	9.7	21.0	24.6	21.6	15.5	5.8
SEER 21, 2013-2017	0.0	1.9	8.3	19.7	25.7	25.5	13.6	5.64

Abbreviations: CI-5 = World Health Organization's IARC Cancer Incidence in Five Continents Volume X; IARC = International Agency for Research on Cancer; SEER 21 = Surveillance, Epidemiology, and End Results 2013-2017 All races, females.

Breast cancer with the HR+/HER2- subtype is more common with increasing age. According to the 2010 US SEER 18 data, 78% of women aged 65 to 74 years had breast cancer with the HR+/HER2- subtype versus 65% of women aged <50 years (Howlader et al. 2014).

Race/Ethnicity

In the United States, the incidence of breast cancer in women is highest among non-Hispanic white women, with the age-adjusted rate (per 100,000) of 130.8, followed by black women (126.7), Hispanic women (93.7), and women who are Asian/Pacific Islander (93.2). However, the incidence of breast cancer in men is higher in black men than in white men (1.8 versus 1.2 per 100,000) (SEER CSR Tables 5.2/6.2).

HR+/HER2- breast cancer is the most common subtype among women of all races/ethnicities, accounting for 76% and 61% of breast cancers in non-Hispanic white women and black women, respectively (ACS 2019).

Risk Factors

Several patient characteristics, clinical risk factors, and behavioural factors have been reported as established or potential risk factors for breast cancer. Some of them are considered nonmodifiable, such as age, race/ethnicity, family history, early menarche (<12 years), late menopause (>55 years), genetic predisposition, and having benign proliferative breast disease and increased mammographic breast density. Factors that are modifiable include alcohol consumption, postmenopausal overweight/obesity, use of menopausal hormone therapy, and breastfeeding (ACS 2019).

Table SI.2 summarises the risk factors that increase the relative risk for female breast cancer (ACS 2019). Although there is less extensive literature on risk factors for male breast cancer, many are similar to those for female breast cancer, including advancing age, *BRCA2* mutations, hormonal imbalance, personal and family history of cancer, and radiation exposure (Abdelwahab Yousef 2017).

Table SI.2. Risk Factors that Increase the Relative Risk for Female Breast Cancer

Relative Risk	Factor
>4.0	▪ Age (65+ vs <65 years although risk increases across all ages until age 80) ▪ Atypical hyperplasia ▪ Lobular carcinoma in situ ▪ Certain inherited genetic mutations for breast cancer (e.g., *BRCA1, BRCA2*)
2.1 to 4.0	▪ Ductal carcinoma in situ ▪ High endogenous oestrogen or testosterone levels (postmenopausal) ▪ High-dose radiation to chest ▪ Mammographically dense breasts ▪ Two or more first-degree relatives with breast cancer diagnosed at an early age
1.1 to 2.0	▪ Alcohol consumption ▪ Early menarche (<12 years) ▪ Obesity (postmenopausal)/adult weight gain ▪ High endogenous oestrogen or testosterone levels (premenopausal) ▪ Late age at first full-term pregnancy (>30 years) ▪ Late menopause (>55 years) ▪ Never breastfed a child ▪ No full-term pregnancies ▪ One first-degree relative with breast cancer ▪ Personal history of endometrial or ovarian cancer ▪ Physical inactivity ▪ Non-atypical ductal hyperplasia or fibroadenoma ▪ Recent and long-term use of menopausal hormone therapy containing oestrogen and progestin ▪ Recent hormonal contraceptive use ▪ Tall height

Citation: Table 4 from American Cancer Society. Breast Cancer Facts & Figures 2019-2020. Atlanta: American Cancer Society, Inc. 2019.

Established breast cancer risk factors are generally associated with HR+/HER2- breast cancer in the same direction established for overall breast cancer risk; however, the impact of some risk factors differs by breast cancer molecular subtype (Valla et al. 2016). Risk factors for which the association is stronger for HR+/HER2- breast cancer include

- nulliparity
- absence of breastfeeding
- increased alcohol consumption

- increased age at menopause
- obesity (premenopausal obesity may be protective, while postmenopausal obesity may increase risk), and
- early menarche (Millikan et al. 2008; Gaudet et al. 2011; Yang et al. 2011; Tamimi et al. 2012; Turkoz et al. 2013; Barnard et al. 2015).

SI.1.4 Main Existing Treatment Options

Early Breast Cancer

Most patients with HR+, HER2- eBC undergo breast surgery with curative intent. Treatments administered before or after breast surgery have the goal to prevent recurrence and death. The decisions for which treatments to administer are often based on multiple factors such as demographics (that is, age), clinicopathological risk factors, and sensitivity to available systemic therapies (that is, HR and HER2 status) (NCCN 2020).

Patients at higher risk of recurrence will often receive more aggressive treatment in the form of chemotherapy (either neoadjuvant or adjuvant) and/or radiotherapy, making up the patient's primary treatment (NCCN 2020).

Many factors are considered when evaluating a patient's risk of breast cancer recurrence. Assessment of risk is commonly defined in clinical practice using anatomical, clinical, and pathological features. The gold standard for the eBC definition of 'high risk' was the Nottingham Prognostic Index, which was the first to introduce the concept of size, grade, and lymph nodes as being the most important factors for determining risk of recurrence (Todd et al. 1987). More tools are now available to help assess risk of disease recurrence and the inclusion of tumour, node, metastasis staging, immunohistochemistry results (for example, ER/progesterone receptor /HER2), tumour grade, and biomarker data combined with surgical findings all factor into the ultimate determination of which patients are at high risk of recurrence and treatment decisions. Patients with lymph node–positive disease are most often candidates for chemotherapy. Standard adjuvant chemotherapy includes an anthracycline and/or taxane-based regimen.

Adjuvant ET is indicated for all patients with detectable ER expression (defined as ≥1% of invasive cancer cells) irrespective of the use of chemotherapy (NCCN 2020). The choice of endocrine agent (tamoxifen and/or 1 of the 3 selective AIs: anastrozole, letrozole, or exemestane) is primarily determined by the patient's menopausal status. All AIs have shown similar antitumour efficacy and toxicity profiles in randomised studies in the adjuvant and preoperative setting. Overall, international clinical guidelines (Saint Gallen International Expert Consensus – Coates et al. 2015; European Society of Medical Oncology [ESMO] – Senkus et al. 2015) and NCCN guidelines align on recommendation of adjuvant ET for at least 5 years, and for postmenopausal patients, AIs should be at least part of ET. For premenopausal patients, standard ET includes tamoxifen with or without ovarian suppression for 5 to 10 years or an AI for 5 years with ovarian suppression in selected patients at high risk of disease recurrence (that is, pre-treated with chemotherapy) based on the TEXT (Pagani et al. 2014) and SOFT (Francis et al. 2018) studies. In postmenopausal patients, use of AIs (both nonsteroidal and steroidal) and tamoxifen sequentially, as monotherapy, or as extended therapy for 5 to 10 years is a valid

option. Treatment of men with breast cancer is similar to that of postmenopausal women, including consideration for androgen suppression with a GnRH analogue.

Based on Reinert and Barrios (2015), approximately 30% of patients with HR+ breast cancer experience distant relapse with metastases following treatment with current standard of care adjuvant therapy. Consequently, there is a critical unmet need for more optimal adjuvant therapy in patients with early HR+ breast cancer who have a high likelihood of distant recurrence. Node-positive HR+, HER2- eBC at high risk of recurrence based on clinical and/or pathological features is a serious disease. There is an unmet medical need to develop new therapies which prevent or reduce the chance of recurrence. When the cancer recurs, it is incurable and recurrent HR+, HER2-breast cancer is life-threatening.

Metastatic/Advanced Breast Cancer

The European School of Oncology-European Society of Medical Oncology (ESO-ESMO) 4th International Consensus Guidelines for Advanced Breast Cancer (ABC4) and NCCN guidelines stipulate that women with Stage IV or recurrent disease characterised by HR+ or HR-/HER2- tumours with no visceral crisis, concern, or proof of endocrine resistance should be treated with ET alone or ET in combination with targeted agents (Cardoso et al. 2018; NCCN 2020). For postmenopausal women with HR+/HER2- recurrent/Stage IV breast cancer, the preferred regimens include a CDK4/6 inhibitor with an AI, fulvestrant with or without a CDK 4/6 inhibitor, or fulvestrant with a nonsteroidal AI. Other recommended regimens include nonsteroidal AIs (anastrozole, letrozole), exemestane, and tamoxifen or toremifene. For premenopausal women, first-line ET includes ovarian suppression/ablation and ET listed previously for postmenopausal women or with a selective ER modulator alone.

If a patient initially responded to ET but eventually progresses, a second or even a third ET may be used to avoid initiation of cytotoxic chemotherapy.

The NCCN recommendations for second-line treatment for postmenopausal women with HR+/HER2- recurrent/Stage IV breast cancer include the preferred option of fulvestrant with a CDK4/6 inhibitor. Other options are fulvestrant with alpelisib (patients with tumour PIK3CA mutations); everolimus with an AI, tamoxifen, or fulvestrant; monotherapy with fulvestrant; nonsteroidal or steroidal AIs; or a selective ER modulator. Most patients with HR+ breast cancer will eventually receive cytotoxic chemotherapy at some point during their treatment, either as initial treatment or following ET. Cytotoxic chemotherapy is recommended for patients with HR+, HER2- mBC that is refractory to ET and/or those with symptomatic visceral disease (NCCN 2020).

In the absence of medical contraindications or patient concerns, anthracycline- or taxane-based regimens, preferably as a single agent, would usually be considered as initial chemotherapy for HER2- mBC in patients who have not received these regimens as adjuvant treatment and for whom chemotherapy is appropriate. In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, single-agent capecitabine, vinorelbine, or eribulin are the preferred choices. Additional choices include gemcitabine and platinum agents.

With some minor variations, breast cancer in men is treated in the same way as breast cancer in women.

SI.1.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

There is limited literature regarding the natural history of untreated breast cancer. Historically, when left surgically undisturbed, breast cancer patients often presented with skin infiltrations and/or skin ulcers, with 67% showing axillary node involvement. These skin ulcers appeared on average 20 months after a tumour was first detected, with growth into the chest wall itself after an additional 2 months. Those who survived 3 years after diagnosis usually saw direct tumour invasion into the second breast, and 25% had metastasis into other vital organs. In the end, only 1 in 20 (5%) survived more than 5 years (Baum 2013). Even when radical mastectomy became a treatment option, only 25% of breast cancer patients survived 10 years (Baum 2013).

In developed countries, about two-thirds of patients with breast cancer present with early stage disease (Stages I/II), while approximately 10% present with advanced disease (Stage III) commonly involving axillary lymph nodes. Distant metastasis at initial presentation is uncommon, arising in about 5% of patients (Lousdal et al. 2014; Akinyemiju et al. 2015; Cancer Research UK).

Survival for breast cancer is strongly related to the stage of the disease at diagnosis. According to data from a UK-based cancer network from 2002 to 2006, the 5-year relative survival for female patients aged 15 to 99 years rapidly decreased from 99% for Stage I, 88% for Stage II, and 55% for Stage III to 15% for Stage IV breast cancer (Cancer Research UK). The 5-year relative survival in US female breast cancer patients from 2007 to 2013 was as follows: localised (99%), regional (85%), and distant stage (27%) (Howlader et al. 2018). Breast cancer survival also varies by molecular subtype, with the overall 5-year survival rates ranging from 77% for the HR-/HER2- subtype to 92% for the HR+/HER2- subtype (ACS 2019).

Although patients treated for ER-positive (ER+) eBC generally have a good prognosis, they remain at risk of recurrence (Pan et al. 2017). The annual risk of recurrence for ER+ early-stage cancers was 9.9% in the first 5 years after initial treatment, with a persistent risk of recurrence after 5 years (5 to 10 years: 5.4%; 10 to 15 years: 2.9%; and 15 to 20 years: 2.8%) (Colleoni et al. 2016). Depending on initial stage, tumour biology, and type of treatment received, nearly 30% of women diagnosed with non-mBC will eventually progress to metastatic disease (O'Shaughnessy 2005; Dawood et al. 2010).

Early breast cancers are typically detected during screening before patients develop any symptoms (ACS 2019). However, most patients diagnosed with HR+/HER2- eBC receive surgery and ET, with some patients at higher risk also receiving adjuvant chemotherapy and/or radiotherapy (Cardoso et al. 2018; NCCN 2020). Therefore, adverse effects or complications associated with the treatments represent important morbidity affecting the eBC patient population. Table SI.3 summarises significant adverse effects and complications associated with early-stage breast cancer treatments.

Table SI.3. Significant Adverse Effects and Complications Associated with Early-Stage Breast Cancer Treatments

Surgery	
Wound complications	Wound infections 1%-2%[a,b] Wound dehiscence <1.5%[b,c] Delayed wound healing 2.2%[a]
Hematoma/seroma	1%-2.5%[a]; 4.5%-9%[b]
Infection (surgical site infection, urinary tract infection, sepsis, and septic shock)	0.4%[c]
Bleeding	0.1%[c]
Respiratory complications (pneumonia, unplanned re-intubation)	0.1%[c]
Thromboembolic complications (PE and DVT requiring therapy)	0.1%[c]
Note: Most surgical complications are perioperative complications, occurring within 30 days of surgery. a De la Cruz et al. 2016. b Browne et al. 2017. c Cil and Cordeiro 2016.	
Radiation	
Acute (occurred ≤3 months)	
Fatigue	18.6%
Radiation dermatitis	44.7%
Pneumonitis	0.7%
Delayed (occurred >3 months)	
Cardiac (including left ventricular failure, cardiac ischemia or infarction, supraventricular arrhythmia, and pericardial effusion)	0.7%
Lymphedema	6.4%
Neuropathy (sensory or motor events)	2.1%
Pneumonitis or pulmonary fibrosis	0.4%
Second cancer (excluding skin and contralateral breast cancers)	10.5%
Note: The rates represent grade ≥2 AEs reported during a median follow-up of 9.5 years in a trial of 1820 eBC patients receiving whole breast irradiation (at a dose of 50 Gy in 25 fractions) with or without regional node irradiation following breast conserving surgery. Majority of the patients were also treated with adjuvant chemotherapy such as anthracycline (85%) and adjuvant endocrine therapy (~75%). Overall, AEs are slightly more frequent with whole breast irradiation plus regional node irradiation compared with whole breast irradiation only, with a notable difference found for pneumonitis (0.2% vs 1.2%), radiation dermatitis (40.1 vs 49.5%), and lymphedema (4.5% vs 8.4%). Source: Whelan et al. 2015	
Endocrine Therapy	
Cardiovascular disease[a,b]	AI: 3.2%-4.2%; Tamoxifen: 2.2%-2.0 (MI only)%
Cerebrovascular disease[a,b]	AI: 1.4%-2.1%; Tamoxifen: 1.4%-1.8%
VTE[a,b]	AI: 2.0%-2.8%; Tamoxifen: 3.8%%
Bone fractures[a,b]	AI: 8.6%-16.7%; Tamoxifen: 5.8%-12.2%
Endometrial cancer[a,b]	AI: 0.2%; Tamoxifen: 0.7%-0.8%
Other second cancers[a,b]	AI: 2.4%-9.3%; Tamoxifen: 2.7%-8.5%
Hypercholesterolaemia[a]	AI: 50.6%; Tamoxifen: 24.6%
Fatigue[b]	AI: 19%; Tamoxifen: 18% ATAC only

Abbreviations: AE = adverse event; AI = aromatase inhibitor (anastrozole or letrozole); DVT = deep vein thrombosis; eBC = early breast cancer; PE = pulmonary embolism; VTE = venous thromboembolic event.

[a] BIG 1-98 is a trial of 4895 (2448 letrozole; 2447 tamoxifen) postmenopausal women with operable invasive breast cancer after a median follow-up of 51 months;

[b] ATAC (2008) is a trial of 6186 (3092 anastrozole; 3094 tamoxifen) postmenopausal women with localised invasive breast cancer after a median follow-up of 100 months.

Source: Coates et al. 2007 (BIG 1-98).

Some patients with mBC may also suffer from long-term complications or late effects from prior breast cancer treatments summarized in Table SI.3.

Meta-analyses of over 40,000 patients with eBC with or without radiotherapy have shown significant increase in cardiac death, and secondary cancers (lung and contralateral breast cancer) more than 10 years after the breast radiotherapy (Taylor et al. 2017). Systemic therapy (for example, anthracycline) also increases a risk of congestive heart failure in a dose-dependent manner (Afifi et al. 2020). Whereas, ET using AIs have been associated with increased serum lipid levels, thus increasing the cardiovascular side effects; and tamoxifen has been associated with increased incidence of stroke and thromboembolic events (Cushman et al. 2003; Bundred et al. 2005; Lewis et al. 2007). The risk of VTE among patients with breast cancer further increases with metastatic disease. In a UK health care data-based study of 13,202 patients with a new diagnosis of breast cancer, the incidence rate (per 1000 person-years) of VTE during the study period was 6.8 for local disease, 9.9 for regional disease; and 18.2 for distant disease (Walker et al. 2016). During the course of a separate UK BC study reporting mortality, 49% of BC patients with VTE died compared to 28% without VTE. For patients with earlier stage of disease, the relative influence of VTE on mortality was greater compared with those for whom the disease had spread (adjusted hazard ratio 2.94 (95% CI 2.29 to 3.77 for local disease, 2.53 (95% CI 2.01 to 3.19) for regional disease) and 1.47 (95% CI 0.82 to 2.63) for distant metastases (Khan et al. 2017).

The symptoms of mBC may vary, depending on the part of the body to which the cancer has spread. Symptoms that are commonly associated with breast cancer metastasis generally include severe, progressive pain; swelling; fracture (if metastasized to the bone); persistent, progressively worsening headache; vision disturbances; seizures; vomiting; nausea (if metastasized to the brain or liver); jaundice; itchy skin or rash; abnormal liver test result; abdominal pain; appetite loss; chronic cough; shortness of breath, and chest pain (if metastasized to the lung). Other nonspecific systemic symptoms of mBC can include fatigue, weight loss, and poor appetite (2016). Based on the data from the primary care records of patients in 11 general practices in the UK between 2002 and 2009, the following clinical features were observed in mBC patients aged ≥ 40 years (n=80): groin pain (10%), pleurisy/pleural effusion (6%), shoulder pain (17%), loss of appetite (20%), vomiting (25%), low back pain (24%), flank/loin pain (11%), chest pain: musculoskeletal (23%), oedema (22%), and abnormal liver enzyme tests (38%). Compared to the matched noncancer controls (n=71), a statistically significant association ($p<0.05$) between the following features and mBC has been identified: vomiting, low back pain, flank/loin pain, chest pain: musculoskeletal, oedema, and abnormal liver enzyme tests (Hamilton et al. 2015). Worldwide, the age-standardized mortality of breast cancer in 2018 was found to be 13.0 per 100,000. The 2018 age-standardized annual mortality rates (per 100,000) were highest in Africa (17.2), followed by Europe (14.9), Oceania (14.8), South America (13.0), North

America (12.6), and Asia (11.3) (Bray et al. 2018). In the US, an estimated 40,610 deaths from breast cancer will occur in 2017, representing 14% of all cancer deaths among women (Siegel et al. 2017). The US age-adjusted mortality rates by different races/ethnicities for the time period 2010 to 2014 were as follows (per 100,000): 30.0 (Blacks), 21.1 (Whites), 14.1 (American Indian/Alaskan native), 14.4 (Hispanic), and 11.3 (Asians/Pacific Islanders) (Siegel et al. 2017).

SI.1.6 Important Comorbidities

Because breast cancer is a disease primarily associated with advancing age, comorbid conditions among breast cancer patients are common (Patnaik et al. 2011).

Table SI.4 summarises prevalence of important comorbidities in patients with breast cancer. Because age is an important predictor of comorbidity, prevalence of comorbid conditions is presented in breast cancer patient populations of varying ages.

Table SI.4. Prevalence of Important Comorbidities in Patients with Breast Cancer

	eBC 18-70 years (Denmark 2001-2004)[a]	Breast cancer 45-84 years (Denmark 1994-2008)[b]	HR+ eBC postmenopausal (Netherlands/Belgium 2001-2006)[c]		Invasive and in situ breast cancer ≥65 years (Netherlands 1997-2004)[d]	Invasive breast cancer ≥66 years (US 1992-2005)[e]
			<70 years	≥70 years		
Comorbidity	**N=4847**	**N=47,904**	**N=2203**	**N=956**	**N=3672**	**N=123,680**
Cardiovascular disorders						
Cardiac arrhythmias				4%	11.6%	
Cardiac valve disorders				3%	4.3%	
Congestive heart failure	2%	1.8%			5.2%	6.9%
Myocardial infarction	1%	1.4%	3%	8%	6.7%	0.8%
Cerebrovascular accident/stroke	1%				7.7%	4.6%
Transient cerebral ischemic attack				4%		
Hypertension			21%	34%	32.1%	
Peripheral arterial disease	1%				2.3%	
Peripheral vascular disease		1.8%				2.7%
DVT					3.0%	
Endocrine disorders						
Hypercholesterolaemia			5%	6%	2.5%	
Diabetes	0%-2%	2.6%	6%	13%		14.5%
Other disorders						
COPD	4%	4.3%	4%	6%	8.9%	9.5%
Liver disease	0-1%	0.1%-0.5%				0.1%
Renal disease		0.4%				1.2%

Abbreviations: COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; eBC = early breast cancer; HR+ = hormone receptor-positive; N = number of patients in the analysis population.

a Guldberg et al. 2017.

b Ording t al. 2013.

c Derks et al. 2019.

d Kiderlen et al. 2014.

e Edwards et al. 2014.

Module SII – Nonclinical Part of the Safety Specification

Abemaciclib was evaluated in Good Laboratory Practice (GLP) nonclinical toxicology and safety pharmacology studies that met or exceeded the recommendations of the International Council for Harmonisation (ICH) S9 guidance, Nonclinical Evaluation for Anticancer Pharmaceuticals. This package of nonclinical studies included repeat-dose toxicology and toxicokinetic, safety pharmacology, developmental and reproductive toxicology, genetic toxicology, carcinogenicity, phototoxicity, and ocular and dermal toxicity/irritancy studies. The genetic toxicity risk of major human metabolites was assessed in separate studies. Studies in which there were no findings relevant to human safety are not discussed in this section.

SII.1 Toxicity

Findings from Repeat-Dose Toxicology Studies

The toxicity profile associated with abemaciclib administration in repeat-dose studies in rats and dogs consisted of bone marrow suppression, GI toxicity, lymphoid tissue effects and male reproductive tract injury (Table SII.1). Morphologic changes in the target organs were consistent with cytotoxic effects in rapidly dividing cells and consisted of pancytopenia in the peripheral blood and bone marrow hypocellularity, crypt hyperplasia and villous atrophy in the GI system, and lymphoid depletion in the thymic cortex and lymph nodes. All of the afore-mentioned changes demonstrated complete or partial reversibility within 28 days of treatment cessation. Based on these findings, patients taking abemaciclib should be informed of the risk and treated symptomatically when appropriate. Effects on the male reproductive tract (hypospermatogenesis and atrophy of the testicular seminiferous epithelium, seminal vesicle, and prostate) were observed in rats and dogs and did not show signs of recovery during the 28-day recovery period; therefore, men should be informed of the risk for infertility when treated with abemaciclib.

In rats, the lung was also identified as a target organ for toxicity, characterised by multifocal alveolar macrophage accumulation with or without reversible bronchoalveolar inflammation. This finding would be consistent with opportunistic infection potentially due to impaired immune function associated with the observed bone marrow and thymic hypocellularity; however, no infectious agents were identified in the lungs of rats. A single rat had minimal lung fibrosis at the end of the recovery period of the 1-month rat study (Day 57); however, no fibrotic changes were observed in rats treated for 3 months. There were no lung effects in dogs. These effects in the rat lung are considered minor, as they did not progress to irreversible changes with increased treatment duration and are likely secondary to immune system effects.

In rodents treated for 3 months or more, the eye was identified as a target organ for toxicity. The following eye effects have been observed in rodents only:

- retinal atrophy: observed in the mouse 3-month study and rat 2-year study
- lens fibre degeneration, also known as cataracts: observed in the rat 6-month study and rat 2-year study
- corneal opacity: observed in the rat 6-month study and
- corneal inflammation: observed in the mouse 2-year study.

Cataracts were associated with elevated glucose. The mechanism of the remaining eye effects is unknown. No information is available on the reversibility of these findings. These findings have not been observed in dog studies or rat studies of less than 6 months' duration; however, no studies of more than 3 months' duration have been completed in dogs.

In rats treated for 6 months, cardiac valves were identified as a target organ for toxicity. This effect was characterised by vacuolated macrophages and inflammation of the cardiac valves. There was no evidence of myxomatous change, haemorrhage, or thickening and no clinical sequalae suggestive of decreased cardiac function. This finding has not been observed in shorter duration rat studies or the 2-year rat study and has not been observed in dog or mouse studies of abemaciclib; however, no studies of more 3 months' duration have been completed in dogs.

Findings from Developmental and Reproductive Toxicology Studies
Abemaciclib was assessed for effects on the developing embryo/foetus in a GLP study in pregnant rats exposed during the period of organogenesis. Increased rates of skeletal and cardiac variations and malformations were observed at exposure similar to average human exposure at 150 mg and 200 mg every 12 hours (Q12H). This increased rate of variations and malformations was accompanied by decreased foetal weights.

Abemaciclib was assessed for effects on fertility in GLP studies in male and female rats. In both studies, no effects on fertility were observed. However, in repeat-dose studies in dogs, rats, and mice, abemaciclib caused damage to the male reproductive tract; therefore, men should continue to be informed of the risk for infertility when treated with abemaciclib.

Nonclinical studies of pre-/postnatal development were not conducted and are not warranted for the intended patient population; however, adequate information is available from repeat-dose, embryo-foetal development and fertility studies to inform patients and prescribers of the potential reproductive and developmental effects and risks from exposure to abemaciclib. Women with reproductive potential should be advised of the risk of reproductive and developmental toxicities and should use highly effective contraception during abemaciclib treatment and for 3 weeks after the last dose. Men should be advised of the risk of infertility from treatment with abemaciclib.

Findings from Carcinogenicity Studies
Abemaciclib was assessed for carcinogenicity in 2-year GLP studies in mice and rats. In rats, abemaciclib caused an increase in interstitial cell hyperplasia and tumours at clinically relevant concentrations. These effects were benign. While interstitial cell tumours in rats commonly do not translate to a human effect based on mechanism, it is unknown whether this observation with abemaciclib in rats will translate to a risk in humans. Men should be advised of the risk of benign interstitial cell hyperplasia and tumours. There were no neoplastic effects observed in female rats or in mice of either sex.

Table SII.1. Key Safety Findings for Nonclinical Studies and Relevance to Humans

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Bone Marrow Suppression: Bone marrow hypocellularity was observed in rats and dogs, affecting all cell lineages.	The nonclinical data indicate that there is a risk for bone marrow injury, possibly resulting in immune suppression, anaemia, and thrombocytopenia. Patients should be advised of this risk and be monitored for it.
Gastrointestinal Toxicity: Crypt hyperplasia and necrosis, epithelial degeneration/atrophy, inflammation, and villous/mucosal atrophy were observed in multiple sections of the gastrointestinal tract in rats and dogs.	The nonclinical data indicate that there is a risk for injury to the gastrointestinal tract. Patients should be advised of this risk and be treated symptomatically.
Lymphoid Tissue Injury: Decreased size/weight of, and lymphoid depletion/hypocellularity in, lymphoid organs (spleen, thymus, lymph nodes) were observed in rats and dogs.	The nonclinical data indicate that there is a risk for negative effects in lymphoid organs, which may translate to immune suppression. Patients should be advised of this risk.
Male Reproductive Tract Injury: Testicular, seminiferous tubule, and epididymal injury was observed in rats and dogs. These effects were not reversible in rats (reversibility not assessed in dogs).	The nonclinical data indicate that there is a risk for reproductive organ injury and fertility effects in men. Men should be advised of this risk.
Reproductive and Developmental Toxicity: Abemaciclib caused increased rates of skeletal and cardiac variations and malformations in rats.	The nonclinical data indicate that there is a risk for reproductive and developmental toxicities in women exposed to abemaciclib during pregnancy. Women of childbearing potential should use highly effective contraception during treatment and for 3 weeks following therapy.
Eye Injury: Lens fibre degeneration (cataracts), retinal atrophy, corneal opacity, and corneal inflammation have been observed in rodents treated for at least 3 months. The reversibility of this effect was not assessed.	The nonclinical data indicate that there is a risk for injury to the eye.
Heart valve inflammation: Vacuolated macrophages in and inflammation of heart valves were observed in rats treated for 6 months. There was no evidence of cardiac functional effects. The reversibility of this effect was not assessed.	The nonclinical data indicate that there is a risk for injury to and inflammation of the heart valve.
Interstitial cell hyperplasia and tumours: Interstitial cell hyperplasia and benign tumours were observed in male rats treated for approximately 2 years.	The nonclinical data indicate that there is a risk of interstitial cell hyperplasia and tumours.

SII.2 Safety Pharmacology

Cardiovascular risk assessment consisted of in vitro assessment of human *ether-à-go-go*-related gene (hERG) potassium channel blockage potential assessment and a cardiovascular safety pharmacology study in dogs. The in vitro hERG study determined that the inhibitory concentration of 50% (IC_{50}) for hERG channel blockage was greater than 1.65 µM, while the human steady-state maximum concentration (C_{max}) at 200 mg Q12H is only 0.62 µM. Corrected

QT interval (QTc) prolongation was not observed in the dog cardiovascular safety pharmacology study; thus, the risk for QTc prolongation to occur in humans is low.

SII.3 Other Toxicity-Related Information or Data

The key safety risks identified by nonclinical data consist of GI injury, bone marrow and lymphoid suppression, reproductive and developmental toxicity, and male reproductive tract injury. There was no evidence of liver effects or injury in nonclinical studies. Serious infection secondary to neutropenia is an Important Potential clinical risk, which is consistent with the observation of bone marrow and lymphoid suppression observed in animals. Reproductive and developmental toxicity have not been confirmed clinically, but are considered important clinically; thus, reproductive and developmental toxicity are Important Potential Risks based on nonclinical data. Interstitial cell hyperplasia and benign tumours, heart valve inflammation and eye effects have not been confirmed clinically. All other nonclinical findings are not considered clinically important.

Module SIII - Clinical Trial Exposure

Abemaciclib has been investigated in patients with advanced cancers, mantle cell lymphoma, breast cancer, non-small-cell lung cancer (NSCLC), brain metastases (secondary to HR+ breast cancer, NSCLC, or melanoma), pancreatic cancer and in healthy subjects.

Clinical trial exposure summaries include all studies in cancer patients for which the primary CSR has been completed. In the included studies, abemaciclib has been used in combination with other therapies.

Table SIII.1. Duration of Exposure

Duration of Exposure	Patients	Person Time (Months)
Cumulative for all Indications		
1 day	5873	68,689
1 month (30 days)	5354	68,384
3 months (91 days)	4457	66,712
6 months (183 days)	3640	63,173
1 year (365 days)	2545	52,770
2 years (730 days)	366	14,361
Total person time	5873	68,689
Note: All completed clinical trials with patients exposed to abemaciclib are included. Source: /lillyce/prd/ly2835219//rmp2020/output/rmp_durexp5.rtf		
HR+, HER2- Early Breast Cancer (Abemaciclib + ET)		
1 day	2788	38,439
1 month (30 days)	2653	38,364
3 months (91 days)	2504	38,086
6 months (183 days)	2359	37,458
1 year (365 days)	1735	31,160
2 years (730 days)	21	513
Total person time for indication	2788	38,439
Source: /lillyce/prd/ly2835219//rmp2020/output/rmp_durexp4.rtf		
HR+, HER2- Locoregionally Recurrent or Metastatic Breast Cancer (Abemaciclib + NSAI)		
1 day	327	7268
1 month (30 days)	311	7256
3 months (91 days)	268	7174
6 months (183 days)	227	6990
1 year (365 days)	187	6628
2 years (730 days)	125	5555
Total person time for indication	327	7268
Source: /lillyce/prd/ly2835219//rmp2020/output/rmp_durexp3.rtf		
HR+, HER2- Locally Advanced or Metastatic Breast Cancer (Abemaciclib + Fulvestrant)		
1 day	441	7905
1 month (30 days)	408	7885
3 months (91 days)	339	7743
6 months (183 days)	286	7510
1 year (365 days)	220	6928
2 years (730 days)	130	5363
Total person time for indication	441	7905

Duration of Exposure	Patients	Person Time (Months)
Source: /lillyce/prd/ly2835219//rmp2020/output/rmp_durexp2.rtf		

Abbreviations: ET = endocrine therapy; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; NSAI = nonsteroidal aromatase inhibitor.

Table SIII.2. Age Group and Gender

Age Group	Patients		Person Time (Months)	
	M	F	M	F
Totals – All Completed Trials				
<65	295	4073	1218	52,933
≥65 and <75	207	1000	881	11,173
≥75 and <85	42	239	185	2192
≥85	0	20	0	107
Total	544	5332	2284	66,404
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_ageexp5.rtf				
HR+, HER2- Early Breast Cancer (Abemaciclib + ET)				
<65	12	2349	153	33,212
≥65 and <75	2	348	114	4131
≥75 and <85	3	69	26	775
≥85	0	4	0	29
Total	21	2770	292	38,147
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_ageexp4.rtf				
HR+, HER2- Locoregionally Recurrent or Metastatic Breast Cancer (Abemaciclib + NSAI)				
<65	N/A	179	N/A	4186
≥65 and <75	N/A	106	N/A	2541
≥75 and <85	N/A	37	N/A	502
≥85	N/A	5	N/A	39
Total	N/A	327	N/A	7268
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_ageexp3.rtf				
HR+, HER2- Locally Advanced or Metastatic Breast Cancer (Abemaciclib + Fulvestrant)				
<65	N/A	287	N/A	5886
≥65 and <75	N/A	113	N/A	1664
≥75 and <85	N/A	38	N/A	350
≥85	N/A	3	N/A	6
Total	N/A	441	N/A	7905
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_ageexp2.rtf				

Note: All completed clinical trials with patients exposed to abemaciclib are included.

Abbreviations: ET = endocrine therapy F = female, HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; M = male; N/A = not applicable; NSAI = nonsteroidal aromatase inhibitor.

Table SIII.3. Dose

Dose of Exposure[a]	Patients	Person Time (Months)
Cumulative for all Indications		
Abemaciclib single agent		
150 mg orally every 12 hours	179	1153
200 mg orally every 12 hours	972	4922
Other (dose escalation or drug-drug interaction)[b]	76	122
Subtotal	1227	6197
Abemaciclib combination therapy		
100 mg orally every 12 hours + LY3023414	3	5
150 mg orally every 12 hours + LY3023414	60	110
200 mg orally every 12 hours + LY3023414	6	2
100 mg orally every 12 hours + pembrolizumab	3	12
150 mg orally every 12 hours + pembrolizumab	17	105
150 mg orally every 12 hours + pemetrexed	8	20
200 mg orally every 12 hours + pemetrexed	15	64
150 mg orally every 12 hours + gemcitabine	3	10
200 mg orally every 12 hours + gemcitabine	21	41
150 mg orally every 12 hours + gemcitabine or pemetrexed	4	16
200 mg orally every 12 hours + gemcitabine or pemetrexed	1	7
150 mg orally every 12 hours + ramucirumab	20	103
200 mg orally every 12 hours + ramucirumab	19	50
150 mg orally every 12 hours + anastrozole	339	2894
150 mg orally every 12 hours + fulvestrant	424	6658
150 mg orally every 12 hours + letrozole	416	7810
150 mg orally every 12 hours + tamoxifen	78	786
150 mg orally every 12 hours + trastuzumab + fulvestrant	78	823
150 mg orally every 12 hours + trastuzumab	96	723
Cumulative for all Indications (Person Time)		
150 mg orally every 12 hours + ET[c]	2791	38,439
150 mg orally every 12 hours + galunisertib	7	13
200 mg orally every 12 hours + anastrozole	16	440
150 mg orally every 12 hours + exemestane + everolimus	15	138
200 mg orally every 12 hours + exemestane + everolimus	4	68
200 mg orally every 12 hours + fulvestrant	121	2177
200 mg orally every 12 hours + letrozole	20	243
200 mg orally every 12 hours + tamoxifen	16	339
200 mg orally every 12 hours + ET[d]	25	163
200 mg orally every 12 hours + exemestane	15	203
150 mg orally every 12 hours + trastuzumab + ET[d]	1	5
200 mg orally every 12 hours + trastuzumab + ET[d]	1	9
200 mg orally every 12 hours + trastuzumab	6	16

Dose of Exposure[a]	Patients	Person Time (Months)
Subtotal	4649	62,491
Total	5876	68,689
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_dosexp5.rtf		
HR+, HER2- Early Breast Cancer (Abemaciclib + ET)		
150 mg orally every 12 hours + ET[c]	2791	38,439
Total	2791	38,439
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_dosexp4.rtf		
HR+, HER2- Locoregionally Recurrent or Metastatic Breast Cancer (Abemaciclib + NSAI)		
150 mg orally every 12 hours + anastrozole	62	1387
150 mg orally every 12 hours + letrozole	265	5880
Total	327	7268
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_dosexp3.rtf		
HR+, HER2- Locally Advanced or Metastatic Breast Cancer (Abemaciclib + Fulvestrant)		
150 mg orally every 12 hours + fulvestrant	320	5728
200 mg orally every 12 hours + fulvestrant	121	2177
Total	441	7905
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_dosexp2.rtf		

Abbreviations: ET = endocrine therapy; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; NSAI = nonsteroidal aromatase inhibitor; Q12H = every 12 hours; Q24H = every 24 hours.

a Patients are counted under the dose to which they were enrolled. Dose adjustments were allowed for toxicities.

b JPBA dose escalation cohort doses included 50, 100, 150, and 225 mg Q24H and 75, 100, and 275 mg Q12H. JPBC dose escalation cohort dose level 1 was 100 mg Q12H. JPBE patients who received only 1 or 2 single 50 mg doses are counted in the 'Other' row; JPBE patients who entered the safety extension are counted in the 200 mg Q12H row. JPCB included Caffeine Citration + Warfarin + Dextromethorphan + Midazolam.

c JPCF: ET included tamoxifen or anastrozole or letrozole or exemestane. Switching ET was allowed during study treatment.

d JPBO: Concomitant endocrine therapy was allowed if certain criteria were met.

Table SIII.4. Ethnic Origin

Ethnic/Racial Origin	Patients	Person Time (Months)
Totals – All Completed Trials		
White	3963	43,789
Black	125	1189
Asian	1433	19,689
American Indian or Alaska Native	98	1410
Native Hawaiian or Other Pacific Islander	4	32
Multiple	36	369
Not Reported	217	2209
Total	5876	68,689
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_raceexp5.rtf		
HR+, HER2- Early Breast Cancer (Abemaciclib + ET)		
White	1933	26,785
Black	57	689
Asian	673	9430
American Indian or Alaska Native	63	786

Ethnic/Racial Origin	Patients	Person Time (Months)
Native Hawaiian or Other Pacific Islander	3	28
Multiple	22	256
Not Reported	40	465
Total	2791	38439
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_raceexp4.rtf		
HR+, HER2- Locoregionally Recurrent or Metastatic Breast Cancer (Abemaciclib + NSAI)		
White	185	3628
Black	5	112
Asian	103	2708
American Indian or Alaska Native	4	77
Multiple	2	9
Not Reported	28	734
Total	327	7268
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_raceexp3.rtf		
HR+, HER2- Locally Advanced or Metastatic Breast Cancer (Abemaciclib + Fulvestrant)		
White	234	3755
Black	9	133
Asian	148	3141
American Indian or Alaska Native	17	455
Multiple	2	66
Not Reported	31	357
Total	441	7905
Source: /lillyce/prd/ly2835219/rmp2020/output/rmp_raceexp2.rtf		

Abbreviations: ET = endocrine therapy; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; NSAI = nonsteroidal aromatase inhibitor.

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

In the abemaciclib clinical development programme, the primary population studied was patients with HR+, HER2- breast cancer; women had to be either postmenopausal or pre-/perimenopausal and rendered postmenopausal by GnRH analogues. All studies had common key exclusion criteria, most of which were intended to ensure safety and minimise risk in a research setting.

Specific and relevant exclusion criteria that are important to abemaciclib are addressed below.

Patient has either a history of central nervous system (CNS) metastasis or evidence of CNS metastasis on the magnetic resonance imaging of brain obtained at baseline.

Reason for exclusion: To minimise confounding factors in safety and efficacy data interpretation.

Is it considered to be included as missing information? No.

Rationale: It should be left to the clinical judgment of the treating physician if the expected treatment benefit with abemaciclib outweighs the potential risk for patients with brain or leptomeningeal metastases. Preclinical data show that abemaciclib distributes efficiently to the brain and, therefore, patients with brain metastasis could potentially receive benefit being treated with abemaciclib.

Patient has a personal history of any of the following conditions: syncope of either unexplained or cardiovascular aetiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest.

Reason for exclusion: Prior conditions could confound expected ADR profile.

Is it considered to be included as missing information? No.

Rationale: It should be left to the clinical judgment of the treating physician if the expected treatment benefit with abemaciclib outweighs the potential risk for patients with pre-existing uncontrolled conditions. In a clinical study to determine the exposure-response relationship between abemaciclib and QT interval in healthy subjects, abemaciclib did not cause clinically significant Fridericia's corrected QT (QTcF) prolongation.

Patient has visceral crisis or lymphangitic spread.

Reason for exclusion: Visceral crisis is not the mere presence of visceral metastases, but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease. For this patient population, combination chemotherapy is recommended.

Is it considered to be included as missing information? No.

Rationale: On advice from the Committee for Medicinal Products for Human Use (CHMP), patients with visceral crisis were excluded from the Phase 3 studies (I3Y-MC-JPBL [MONARCH 2] and I3Y-MC-JPBM [MONARCH 3]).

Patient is a pregnant or lactating woman.

Reason for exclusion: Studies in animals have shown reproductive toxicity (see Module SII). Abemaciclib is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether abemaciclib is excreted in human milk. A risk to newborns/infants cannot be excluded. Patients receiving abemaciclib should not breastfeed.

Is it considered to be included as missing information? No

Rationale: Labelling information will clearly indicate that use of abemaciclib in women who are pregnant or breastfeeding is not recommended and women of childbearing potential should use contraception.

SIV.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 and/or cumulative exposure. This applies to the I3Y-MC-JPCF (monarchE) data included; although the median duration of follow-up was 76 months, no new safety signals or adverse reactions were identified following final overall survival analysis of monarchE study.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure (Persons)
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
Hepatic impairment	Total of 25 patients
Mild	9 patients
Moderate	10 patients
Severe	6 patients
Renal impairment	Total of 507 patients
Mild (60 mL/min ≤ CGCL <90 mL/min)	381 patients
Moderate (30 mL/min ≤ CGCL <60 mL/min)	126 patients
Severe	Not included in the clinical development programme
Cardiovascular impairment	Not included in the clinical development programme
Immunocompromised patients	Not included in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Subpopulations with people carrying relevant genetic polymorphisms	Not included in the clinical development programme
Population with relevant different ethnic origin	Clinical trials enrolled patients of various racial and/or ethnic origins, and there were no restrictions outlined in clinical protocols. Studies specifically conducted in Japan enrolled only Japanese patients, per protocol inclusion criteria. Per data presented in Module SIII, the distribution of ethnic origins enrolled in trials is generally reflective of the anticipated target population. While the toxicity pattern was consistent with the overall population, Asian patients experienced more myelosuppression and ALT/AST increase in monarchE and MONARCH 2 and 3. In monarchE, Asian patients were also shown to experience more myelosuppression and ALT/AST. In addition, Asian patients in monarchE experienced more stomatitis, nasopharyngitis, and urinary tract infections, while white patients experienced more fatigue and gastrointestinal toxicities. ILD/pneumonitis in the experimental arm was more frequent in the Asian patients, though the incidence of Grade ≥3 events was consistent across races

Type of Special Population	Exposure (Persons)
	There is no additional evidence to suggest that there are gene variances or mutations that could impact drug metabolism/PK/adverse drug reaction (ADR) due to the nature of abemaciclib.
Other	The number of elderly patients (≥65 years) in MONARCH 2 is lightly lower than the overall metastatic breast cancer population; however, in MONARCH 3 the proportion is reflective of the overall metastatic breast cancer population. This may be due to the varying severity of breast cancer in these trials. Also, the proportion of elderly patients in monarchE was lower than in the overall population with HR+, HER2- at diagnoses, possibly because younger patients tend to present with more aggressive tumours. There has been no indication that patients ≥65 years are at greater risk of adverse events than patients <65 years. No dose reductions other than those recommended for all patients are considered necessary. The safety and efficacy of abemaciclib in children and adolescents (<18 years) have not been established. No data are available. Men with early breast cancer were eligible to participate in monarchE, and a total of 21 men received abemaciclib. Although the number of male patients is low, the safety profile of abemaciclib in men is consistent with the profile seen in women.

Note: Hepatic impairment based on Child-Pugh classification of hepatic impairment (Child and Turcotte 1964; Pugh et al. 1973).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CGCL = Cockcroft-Gault creatinine clearance; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; ILD = interstitial lung disease; PK = pharmacokinetics.

Sources: JPBV CSR, Sections 5.3 (Study Design) and 6.1 (Demographics), m_o_ae_summ_unified; m_c_ae_overview_4; m_o_ae_pt_soc_bymaxgrad_3; lbmaxgrad.rtf

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide sales of abemaciclib have been collected for the cumulative period ending on 31 August 2025.

Patient exposure estimates for abemaciclib are calculated by dividing the total number of milligrams sold by the defined daily dose to obtain the total days of therapy. The total days of therapy are then divided by the estimated average length of therapy for an individual patient to obtain the estimated number of patients exposed or 365 days to obtain the estimated number of patient-years of exposure to abemaciclib.

Inputs for the patient exposure estimate were as follows:

- Amount sold (mg): Lilly global sales data for abemaciclib.
- Defined daily dose: 300 mg.
- Average length of therapy = 9.9 months (297 days). This was based upon IQVIA APLD claims data for abemaciclib over the period of this report. There can be significant variance in the length of therapy based upon the indication.

SV.1.2 Exposure

During the cumulative period ending on 31 August 2025, 44 861 121 700 milligrams were sold worldwide. An estimated 503 400 patients were exposed to abemaciclib with 409 600 patient-years of exposure. Table SV.1 provides a summary of worldwide sales and estimated patient exposure.

Table SV.1. Cumulative Geographical Summary of Sales and Estimated Patient Exposure for Abemaciclib through 31 August 2025

Region	Sales (milligrams)	Estimated Patient Exposure (Patients)	Estimated Patient Exposure (Patient-Years)
Europe	13 250 402 900	148 700	121 000
United States	7 637 688 700	85 700	69 700
Japan	4 821 244 500	54 100	44 000
Other Countries	19 151 785 500	214 900	174 900
Global Totals[a]	**44 861 121 700**	**503 400**	**409 600**

[a] Totals may not sum due to independent rounding.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Abemaciclib has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behaviour, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which an anticancer drug will be misused, diverted, and/or abused once marketed. Like any drug, if stolen, abemaciclib has a potential for misuse.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all ADRs for abemaciclib when administered as a single agent or in combination with ET represent a risk per the guidelines on GVP Module V (Revision 2), based on their severity and clinical outcome (for example, cases presented with Grade ≥3 AEs and/or cases leading to discontinuation of trial medication). Therefore, this section focuses on those ADRs that are considered a risk, but not an important risk.

- TEAEs of pneumonitis are of interest, as they require timely detection and management.
- Nonclinical findings showed minimal lung fibrosis in a single rat only, with no fibrotic changes in animals treated for 3 months. These effects in the rat lung were considered minor, with no progression to irreversible changes with increased duration of treatment, and are likely secondary to immune system effects.
- In the reported clinical trials, the incidence of pneumonitis was low, predominantly of Grade 1 or Grade 2. Diagnosis and causal association with abemaciclib are difficult to establish due to clinical confounding factors such as cancer spread to the lungs, prior exposure to radiation, presence of infection and administration of comedication in some patients. Therefore, the low incidence of cases with no confirmed causality, mainly nonserious, does not indicate an important risk, and pneumonitis is not considered an adverse reaction.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk-Benefit Impact:

Important Identified Risk 1: Venous Thromboembolic Events (VTEs)

In the randomised Phase 3 studies (MONARCH 2 and MONARCH 3), there were a greater number of patients who experienced VTEs in the abemaciclib plus ET arm than in the placebo plus ET arm.

In most of these cases, severity was reported as Grade 1, 2, or 3, and VTEs were treated with standard anticoagulation therapy (low molecular-weight heparin). In few cases only, treatment with abemaciclib was discontinued due to VTE.

Risk-Benefit Impact:

The VTEs comprise mainly pulmonary embolism and deep vein thrombosis; the latter occurs most often in the leg, but other veins such as in the arm and cerebral veins can also be affected (Di Nisio et al. 2016). The VTEs are determined to be ADRs for abemaciclib when administered in combination with ET. Per reported Common Terminology Criteria for Adverse Events assessment, the majority of VTEs were uncomplicated, isolated cases with severe outcome (including fatal cases). Treatment consisted of standard anticoagulation therapy (low molecular-weight heparin). Generally, these events did not result in discontinuation of the study drug. These data suggest that the risk-benefit impact is low.

For routine and additional PV activities, see Part III.

Important Potential Risk 1: Serious Infection Secondary to Neutropenia

The TEAE of neutropenia has been very commonly reported in clinical studies with single-agent abemaciclib and when combined with ET, and was predominantly of low-grade severity. Across studies, neutropenia was observed early in the treatment course, within the first 2 months, and maintained over the course of treatment. On central laboratory analysis, neutrophil count decrease from the baseline visit was observed, mean neutrophil counts generally remained stable at the later visits, and the reduced counts were reversible once patients discontinued from treatment. Febrile neutropenia was infrequent and not associated with severe infection.

Generally, patients with neutropenia are more susceptible to bacterial infections.

The TEAEs in the infection and infestations System Organ Class reported in the abemaciclib clinical development programme were predominantly low-grade infections (upper respiratory tract infection and urinary tract infection were the most common infections in all 3 registration studies).

Based on available data from the abemaciclib clinical programme, there does not appear to be a relationship between severe neutropenia and concurrent infection.

Risk-Benefit Impact:

Neutropenia is determined to be an ADR for abemaciclib when administered as a single agent and in combination with ET. Infections, including the most commonly reported events of upper respiratory tract infection and urinary tract infection, are determined as ADRs for abemaciclib when combined with ET.

The majority of infections reported in the clinical programme were of low-grade severity; furthermore, only a few patients discontinued treatment due to infections. Based on the frequency of reported events and their potential severe outcome, severe infections secondary to neutropenia are considered an important risk. The low grade of severity in the majority of events of infections reported, and the apparent lack of relationship between neutropenia and severe infections, led to the conclusion that this represents a potential risk.

These data suggest that the risk-benefit impact is low.

For routine and additional PV activities, see Part III.

Important Potential Risk 2: Liver Injury

In the randomised Phase 3 studies (MONARCH 2 and MONARCH 3), there was a higher incidence of increased ALT and AST, both TEAEs and on central laboratory analysis, in the abemaciclib plus ET arm than in the placebo plus ET arm. These were predominantly of Grade 1 or Grade 2; a concurrent increase in blood bilirubin was infrequent. Generally, ALT and AST increases were manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment.

The ALT increases, especially when combined with increases of bilirubin, may be indicative of severe liver injury. Since ALT is found predominantly in the liver, whereas AST is also found in various other organs besides the liver, ALT is considered to be more specific to the liver.

Risk-Benefit Impact:

The ALT and AST increases are determined to be ADRs for abemaciclib when administered in combination with ET.

Generally, these increases were manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment. Several patients had isolated episodes of elevated ALT and AST that resolved without dose adjustment.

The majority of ALT increase events were of low severity and not accompanied by increases in bilirubin. These events were managed by dose modification and other standard management techniques. The lack of serious outcomes, that is, severe liver injury as indicated by increases of ALT and/or AST combined with increases of bilirubin, in patients experiencing ALT increases led to the conclusion that this risk represents a potential risk.

Considering the low incidence of severe ALT increases and serious hepatic events observed in the clinical development programme, the risk-benefit impact appears to be low.

For routine and additional PV activities, see Part III.

Important Potential Risk 3: Reproductive and Developmental Toxicities

Based on findings in animals, abemaciclib has the potential to cause foetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased foetal weight at maternal exposures that were similar to human clinical exposure based on the area under the concentration versus time curve (AUC) at the recommended human dose.

Pregnant women were excluded from participation in clinical trials with abemaciclib; therefore, there are no available human data informing the potential drug-associated risk.

Risk-Benefit Impact:

Animal studies indicate the potential of abemaciclib to harm offspring when administered to humans at recommended doses. This important risk has been addressed in the clinical

development programme of abemaciclib by ensuring that pregnant women are not exposed to this drug.

Consequently, this will be addressed in clear language incorporated in the labelling to direct the treating physician's attention to this risk.

Missing Information 1: Exposure and safety in patients with severe renal impairment

Abemaciclib and its metabolites are not significantly renally cleared. Based on population pharmacokinetic (PopPK) modelling, dose adjustment is not necessary in patients with mild or moderate renal impairment. There are no data in patients with severe renal impairment or in patients on dialysis to provide any dose adjustment recommendation.

Risk-Benefit Impact:

Patients with severe renal impairment have been excluded from participation in the abemaciclib clinical development programme; therefore, no data in humans are available.

Pharmacologic properties indicate that renal function is not significantly involved in the clearance of abemaciclib. There is no indication from nonclinical studies that renal toxicity is considered clinically important.

Use of abemaciclib in patients with severe renal impairment is not contraindicated. Abemaciclib should be administered with caution in patients with severe renal impairment.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

GVP Module V (Revision 2) 'Risk Management Systems' (EMA/838713/2011 Rev 2) and the accompanying document 'Guidance on the format of the risk management plan (RMP) in the EU – in integrated format' (EMA/164014/2018 Rev.2.0.1, effective 21 October 2018) clarify the criteria for a risk and the factors which define a risk as being important. Lilly has performed a cumulative evaluation of the risks listed as safety concerns in the current abemaciclib EU RMP (Version 0.4) to determine whether they still fulfil the criteria for safety concerns. Following review of the additional clinical trial data from the Phase 3 pivotal study monarchE (I3Y-MC-JPCF) and approximately 2 years post-marketing safety data for abemaciclib since the final sign-off date of the previous EU RMP (29 June 2018), Lilly is reclassifying the following risks.

Venous Thromboembolic Events – Important identified risk removed as a safety concern

The important identified risk of VTEs has been removed from the list of safety concerns. Lilly was requested to include VTE as an important identified risk in the EU RMP by the Pharmacovigilance Risk Assessment Committee during the initial MAA in the EU on the basis of data from the randomised Phase 3 studies MONARCH 2 (I3Y-MC-JPBL) and MONARCH 3 (I3Y-MC-JPBM).

VTEs are a recognised ADR for abemaciclib in combination with ET. VTEs are considered to be fully characterised based on the additional data from the monarchE study, including an additional

2791 patients treated with abemaciclib in combination with ET. Cancer patients are at higher risk of developing VTEs irrespective of treatment, and the increased risk of VTEs in the target population treated with abemaciclib in combination with ET is judged acceptable in relation to the severity of the indication treated. VTEs are addressed by appropriate language in the product information, and management of VTE is part of standard clinical practice. No additional risk minimisation measures or PV activities are required. As such, in accordance with GVP Module V (Revision 2), Lilly considers VTEs to be a non-important identified risk which can be removed as safety concern from the EU RMP for abemaciclib.

From a review of 3 completed Phase 3 controlled clinical trials (MONARCH 2, MONARCH 3, and monarchE), the incidence of VTEs in the abemaciclib plus ET arm ranged from 2.3% to 6.1% for any grade events and from 1.2% to 3.1% for severe (Grade ≥3) VTEs, with the highest incidence reported in MONARCH 3. Grade 4 (life-threatening) and Grade 5 (fatal) VTEs were uncommon (<1%) across all 3 studies. In monarchE, no fatal VTEs occurred in abemaciclib-treated patients. VTEs were well managed with anticoagulants and did not affect patients' ability to continue study treatment, as attested by the low rate (range 0.4% to 1.2%) of study treatment discontinuation due to VTE, with 0.4% patients discontinuing study treatment due to VTE in monarchE.

Abemaciclib was first authorised on 28 September 2017, and through 29 February 2020, has an estimated post-marketing exposure of 27 100 patients. The cumulative reporting rate of VTEs from post-marketing sources up to the data lock point of this RMP (28 March 2020) is low (0.2%), with a fatal outcome in 1.9% of cases.

Based on the totality of the data, including new data from monarchE collected from an additional 2791 patients treated with abemaciclib in combination with ET (comprising 45% of the total 6172 patients who have received abemaciclib in the developmental programme cumulatively through 27 March 2020), and a post-marketing exposure of more than 27 000 patients, Lilly considers VTE to be fully characterised. Oncology physicians are aware of this ADR, and diagnosis and treatment of VTE is part of standard clinical practice. VTE is adequately addressed by language in the product information, and no additional risk minimisation measures or additional PV activities have been undertaken.

It is acknowledged that, according to GVP Annex I – Definitions (Revision 4), normally any risk included in the warnings and precautions section of the product information should be considered important. However, the guidance states that the importance of that risk is also determined by other factors including the seriousness of the risk, the impact on public health, and the impact on risk-benefit balance. The current warning and precaution in the SmPC pertaining to VTE will remain unchanged as a result of this update and is considered sufficient to inform health care professionals of this ADR. VTEs will continue to be reviewed as part of routine PV activities.

Serious Infection Secondary to Neutropenia – Important potential risk removed as a safety concern

The important potential risk of serious infection secondary to neutropenia has been removed from the list of safety concerns. Lilly included serious infection secondary to neutropenia as an important potential risk in the EU RMP during the initial MAA in the EU on the basis of data from clinical studies with single-agent abemaciclib and the randomised Phase 3 studies MONARCH 2 and MONARCH 3.

Neutropenia is a recognised ADR for abemaciclib in combination with ET. Severe neutropenia can lead to serious infective complications resulting in significant morbidity and mortality. However, data from Phase 3 controlled clinical trials (MONARCH 2, MONARCH 3, and monarchE) revealed a low (<2%) incidence of febrile neutropenia in the abemaciclib plus ET arm across all 3 studies. Severe (Grade ≥3) infection occurring in association with Grade ≥3 neutropenia was infrequent (<1%) and observed only in MONARCH 2, with no cases identified in abemaciclib-treated patients in MONARCH 3 or monarchE. Overall, no apparent relationship was demonstrated between Grade ≥3 neutropenia and the occurrence of severe infection in the abemaciclib development programme. Based on the additional data from the monarchE study, the risk of serious infection secondary to neutropenia is considered fully characterised. Neutropenia and infections are addressed by appropriate language in the product information and managed as part of standard clinical practice. Therefore, Lilly proposes to remove serious infection secondary to neutropenia as safety concern from the EU RMP for abemaciclib.

From a review of 3 completed Phase 3 controlled clinical trials (MONARCH 2, MONARCH 3, and monarchE), the incidence of Grade ≥3 neutropenia in the abemaciclib plus ET arm ranged from 18.6% to 26.5% for TEAEs and from 18.1% to 32.1% for treatment-emergent laboratory abnormalities, with the highest incidence for both parameters reported in MONARCH 2. In the Phase 3 studies, the incidence of Grade ≥3 neutropenia TEAEs in abemaciclib-treated patients was primarily driven by Grade 3 events (range 18.0% to 23.6%), with Grade 4 neutropenia ranging from 0.6% to 2.9%; febrile neutropenia was infrequent (range 0.3% to 1.4%). In monarchE, febrile neutropenia occurred in 7 patients (0.3%) in the abemaciclib plus ET arm. Across the Phase 3 studies, neutropenia AEs were well managed with protocol-specified abemaciclib dose modifications and use of granulocyte-colony stimulating factor per standard supportive care, with study treatment discontinuation due to any grade neutropenia reported in <2% of patients in the abemaciclib plus ET arm.

The incidence of severe (Grade ≥3) infections in patients treated with abemaciclib in combination with ET in the 3 MONARCH studies ranged from 4.4% to 8.3%. However, severe infection secondary to neutropenia (defined as Grade 3 or higher infection concurrent with, or occurring within, a week of Grade 3 or 4 treatment-emergent neutropenia) was infrequent (<1%). Across the Phase 3 MONARCH studies, Grade ≥3 infection with coinciding Grade 3 to 4 TEAE neutropenia or Grade 3 to 4 laboratory abnormalities of decreased neutrophil count occurred in 3 patients (0.7%) and 1 patient (0.2%), respectively, in the abemaciclib plus ET arm of MONARCH 2. In monarchE, in the 519 patients experiencing Grade ≥3 neutropenia TEAEs,

49 patients had temporally associated infections, all of which were maximum Grade 1 and 2. Temporal association analyses in the Phase 3 studies demonstrated no relationship between neutropenia and severe infection.

Abemaciclib was first authorised on 28 September 2017, and through 29 February 2020, has an estimated post-marketing exposure of 27 100 patients. The cumulative reporting rate of serious infection secondary to neutropenia from post-marketing sources up to the data lock point of this RMP (28 March 2020) is low (0.7%), with a fatal outcome in 10.5% of cases.

Based on the totality of the data, including new data from monarchE with an additional 2791 patients treated with abemaciclib in combination with ET (comprising 45% of the total 6172 patients who have received abemaciclib in the development programme cumulatively through 27 March 2020), and a post-marketing exposure of more than 27 000 patients, Lilly considers the risk of serious infection secondary to neutropenia to be fully characterised. Neutropenia and infections are adequately addressed by language in the label, and no additional risk minimisation measures have been undertaken. Oncology physicians are aware of the higher risk of infections in cancer patients, and diagnosis and management of neutropenia/infection is part of standard clinical practice.

The current warnings and precautions in the SmPC pertaining to neutropenia and infections/infestations will remain unchanged as a result of this update and are considered sufficient to inform health care professionals of these events. Cases of serious infection secondary to neutropenia will continue to be reviewed as part of routine PV activities.

Liver Injury – Important potential risk removed as a safety concern

The important potential risk of liver injury has been removed from the list of safety concerns. Lilly included liver injury as an important potential risk in the EU RMP during the initial MAA in the EU on the basis of data from the randomised Phase 3 studies MONARCH 2 and MONARCH 3.

Lilly acknowledges that ALT increased and AST increased are ADRs for abemaciclib in combination with ET and that elevated transaminases may indicate underlying liver injury. However, based on review of data from 3 completed controlled Phase 3 clinical trials (MONARCH 2, MONARCH 3, and monarchE), the majority of patients treated with abemaciclib plus ET who developed elevated transaminases had low-grade and isolated increases in ALT/AST without concurrent elevated serum bilirubin. Across the Phase 3 studies, few patients experienced elevations in ALT and/or AST ≥3X ULN together with total bilirubin >2X ULN indicative of clinically relevant liver injury. From a comprehensive analysis of laboratory liver function tests and clinical data from more than 2700 patients who received abemaciclib plus ET in monarchE, no cases of drug-induced liver injury were identified. Based on the totality of the data, there is insufficient evidence to suggest that the transaminase increases commonly associated with abemaciclib represent clinically significant liver injury, and the risk is deemed to be fully characterised. Therefore, Lilly proposes to remove liver injury as a safety concern from the EU RMP for abemaciclib.

From a review of 3 completed Phase 3 controlled clinical trials (MONARCH 2, MONARCH 3, and monarchE), the majority of patients in the abemaciclib plus ET arm experienced low-grade (Grade 1 to 2) TEAEs and laboratory abnormalities of increased ALT and AST. The incidence of Grade ≥3 ALT increased in the abemaciclib plus ET arm across the MONARCH studies ranged from 2.3% to 6.4% for TEAEs and from 2.2% to 8.0% for treatment-emergent laboratory abnormalities, with the highest incidence for both parameters reported in MONARCH 3. Grade 4 increased ALT (TEAEs and laboratory abnormalities) were infrequent (<1%) in all 3 studies. The number of abemaciclib-treated patients in the MONARCH studies who met the criteria of treatment-emergent ALT or AST ≥3X ULN and bilirubin >2X ULN suggestive of potential drug-induced liver injury was low (MONARCH 2: n=2; MONARCH 3: n=1; monarchE: n=8). No cases of drug-induced liver injury were identified in the 8 patients in monarchE who had elevated ALT or AST >3X ULN and total bilirubin >2X ULN following Lilly medical case assessment.

Overall, hepatic events observed in the abemaciclib plus ET arm of the Phase 3 studies were predominantly isolated transaminase increases of low-grade severity and not associated with elevated bilirubin, manageable with dose modifications, and resolved either upon discontinuation of study treatment or without intervention. There was no evidence for clinically relevant drug-induced liver injury or hepatic failure related to abemaciclib.

Abemaciclib was first authorised on 28 September 2017, and through 29 February 2020, has an estimated post-marketing exposure of 27 100 patients. The cumulative reporting rate of liver injury events from post-marketing sources up to the data lock point of this RMP (28 March 2020) is low (1.3%), with a fatal outcome in 1.4% of cases.

Based on the review, including an additional 2791 patients treated with abemaciclib in combination with ET in monarchE (comprising 45% of the total 6172 patients who have received abemaciclib in the development programme cumulatively through 27 March 2020) and a post-marketing exposure of more than 27 000 patients, there are insufficient data to suggest that transaminase increases commonly associated with abemaciclib are indicative of clinically significant liver injury. Transaminase elevations related to abemaciclib are considered adequately characterised and appropriately addressed by language in the product information. No additional risk minimisation measures have been undertaken.

The current warnings and precautions pertaining to increased aminotransferases in the SmPC will remain unchanged as a result of this update and are considered sufficient to inform physicians of hepatic events. Hepatic events including liver injury/failure will continue to be reviewed as part of routine PV activities.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: None

Important Potential Risk: Reproductive and Developmental Toxicities

Potential mechanisms:

Inhibiting CDK4 and CDK6 prevents cell cycle progression through the G1 restriction point (Sherr 1996; Ortega et al. 2002). As embryo-foetal development requires mitosis, abemaciclib likely inhibits embryo-foetal development. While definitive studies to confirm this mechanism of action have not been conducted, the observations of teratogenicity and decreased foetal weights in rats treated during the period of organogenesis are consistent with this potential mechanism.

Evidence source(s) and strength of evidence:

Nonclinical data indicate that there is a risk for reproductive and developmental toxicities in women exposed to abemaciclib during pregnancy and a risk for reproductive organ injury and fertility effects in men. Accordingly, this has been determined a key safety finding from the nonclinical development programme of abemaciclib.

Pregnant women are excluded from participation in the clinical development programme for abemaciclib; women of childbearing potential were required to use highly effective contraception during participation in any clinical trial. Therefore, no human data are available.

Characterisation of the risk:

Nonclinical data have determined this safety concern as a key safety finding.

In study monarchE, following approximately 1 year of treatment with abemaciclib and tamoxifen, 1 patient discontinued GnRH analogue therapy and despite barrier contraception and an intrauterine device in place, became pregnant. Study treatment was stopped at approximately 19 weeks gestation when pregnancy was confirmed. There were no complications during the pregnancy, and the patient had a successful delivery at 39 weeks gestation. No congenital or chromosomal abnormalities were detected.

No pregnancies were reported in MONARCH 2 or MONARCH 3, and no other data are available from other completed or ongoing abemaciclib clinical trials.

Post-marketing Data – up to 28 March 2020 estimated exposure 27 100 patients:

No data reported

Risk factors and risk groups:

The effects of maternal cancer on foetal and infant health may include malnutrition, hypoxia, chronic inflammation, and toxic or teratogenic effects of cancer treatment (Lu et al. 2017). Additional risk factors associated with reproductive and developmental outcomes are listed below.

- For maternal infertility: temporary or permanent amenorrhea and decreased fertility due to chemotherapy (Partridge et al. 2004) and ovarian damage and uterine damage due to radiation exposure (Meirow et al. 2010).
- For spontaneous abortion (miscarriage): for example, previous miscarriage, termination and infertility, assisted conception, regular/high alcohol consumption, feeling stressed, higher maternal and paternal age (Maconochie et al. 2007).
- For stillbirth: for example, parity, ethnicity, maternal obesity, smoking, pre-existing diabetes, history of mental health problems, antepartum haemorrhage, and foetal growth restriction (Gardosi et al. 2013).
- For congenital anomalies and teratogenicity: certain maternal factors such as alcohol consumption, folic acid deficiency, uncontrolled maternal diabetes or phenylketonuria, obesity, and advanced maternal age (Harris et al. 2017); certain medications used to treat cancer (for example, cytarabine, 5-fluorouracil, cyclophosphamide, tamoxifen, imatinib; Voulgaris et al. 2011) or other medical conditions (for example, antiepileptic drugs, folic acid antagonists; Battino 2017; Harris et al. 2017).

Preventability:

Advise pregnant women of the potential risk to the foetus. Women of childbearing potential should use highly effective contraception during treatment and for 3 weeks following therapy. Abemaciclib is not recommended during pregnancy or in women of childbearing potential not using contraception.

Impact on the risk-benefit balance of the product:

Based on findings from nonclinical studies, any exposure to abemaciclib during pregnancy may have severe consequences for the foetus. This risk, and appropriate risk minimisation measures, is clearly addressed in respective sections of the label.

Public health impact:

The public health impact is considered minimal, as the use of abemaciclib should be avoided during pregnancy, and due to the low pregnancy rates expected in the indicated population.

SVII.3.2 Presentation of the Missing Information

Missing Information: Exposure and safety in patients with severe renal impairment

Evidence source:

Patients with severe renal impairment were excluded from the abemaciclib clinical development programme. Pharmacologic properties indicate that renal function is not significantly involved in the clearance of abemaciclib. Based on these findings, the safety profile of patients with severe renal impairment is not expected to be different from that in the general target population. There is no indication from nonclinical studies that renal toxicity is considered clinically important.

Population in need of further characterisation:

Use of abemaciclib in patients with severe renal impairment is not contraindicated. Abemaciclib should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity. If any data about patients with severe renal impairment and their effect on the risk-benefit profile become available, they will be assessed as part of routine PV activities.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Reproductive and developmental toxicity
Missing information	Exposure and safety in patients with severe renal impairment

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

None.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Reproductive and developmental toxicity	**Routine risk communication:** SmPC Sections 4.1 and 4.6 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for pre-/perimenopausal women who are administered with abemaciclib in combination with endocrine therapy are included in SmPC Section 4.1. • Recommendations for women of childbearing potential are included in SmPC Section 4.6. **Other routine risk minimisation measures beyond the Product Information:** None
Exposure and safety in patients with severe renal impairment *(Missing information)*	**Routine risk communication:** SmPC Sections 4.2 and 5.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations and information for administering abemaciclib in patients with severe renal impairment are in SmPC Section 4.2 **Other routine risk minimisation measures beyond the Product Information:** None

Abbreviation: SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Sections 4.1 and 4.6 • Recommendations for pre-/perimenopausal women who are administered with abemaciclib in combination with endocrine therapy are included in SmPC Section 4.1. • Recommendation for women of childbearing potential are in SmPC Section 4.6.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Exposure and safety in patients with severe renal impairment *(Missing information)*	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2 • Recommendations and information for administering abemaciclib in patients with severe renal impairment are in SmPC Sections 4.2 and 5.2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Abbreviation: SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for VERZENIOS (abemaciclib)

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

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

I - The Medicine and What It is Used for

VERZENIOS is authorised for locally advanced or mBC (see SmPC for the full indication). It contains abemaciclib as the active substance and it is given orally as immediate release film-coated tablets: 50, 100, and 150 mg.

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

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of VERZENIOS, together with measures to minimise such risks and the proposed studies for learning more about VERZENIOS's risks, 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 package leaflet and SmPC 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 (e.g., with or without prescription) can help to minimise its risks.

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

If important information that may affect the safe use of VERZENIOS is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of VERZENIOS 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 VERZENIOS. 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 (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Reproductive and developmental toxicity
Missing information	Exposure and safety in patients with severe renal impairment

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Potential Risk: Reproductive and Developmental Toxicity	
Evidence for linking the risk to the medicine	Abemaciclib works by interfering with a certain step in cell division. Because foetal development requires cell division, it is likely that abemaciclib inhibits foetal development. In rats, lower foetal weight and other effects were observed, which is consistent with the classification of this risk as a potential risk.
Risk factors and risk groups	Chemotherapy exposure during pregnancy carries a higher risk of spontaneous abortion and major birth defects. Older patients (>40 years) are more likely to develop early menopause after chemotherapy. Additional risk factors include smoking, drinking alcohol, diabetes, and obesity.
Risk minimisation measures	Abemaciclib is not recommended during pregnancy or in women of childbearing potential who are not using contraception. Women of childbearing potential should use a highly effective birth control method during treatment and for 3 weeks following treatment.
Missing Information: Exposure and Safety in Patients with Severe Renal Impairment	
Risk minimisation measures	Use of abemaciclib in patients with severe renal impairment is not contraindicated. Abemaciclib should be administered with caution in patients with severe renal impairment. Complete blood counts should be monitored before starting abemaciclib therapy and every 2 weeks for the first 2 months of therapy. [Routine risk minimisation measures]

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of VERZENIOS.

II.C.2 Other Studies in Post-Authorisation Development Plan

Not applicable.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

None

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

None.