PROFESSIONAL INFORMATION

S4

1. NAME OF THE MEDICINE

YULAREB 50 mg Film-coated tablet

YULAREB 100 mg Film-coated tablet

YULAREB 150 mg Film-coated tablet

YULAREB 200 mg Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

YULAREB 50 mg - Each film-coated tablet contains 50 mg abemaciclib

YULAREB 100 mg - Each film-coated tablet contains 100 mg abemaciclib

YULAREB 150 mg - Each film-coated tablet contains 150 mg abemaciclib

YULAREB 200 mg - Each film-coated tablet contains 200 mg abemaciclib

Excipient with known effect:

Contains sugar

Each 50 mg film-coated tablet contains 14 mg of lactose monohydrate

Each 100 mg film-coated tablet contains 28 mg of lactose monohydrate

Each 150 mg film-coated tablet contains 42 mg of lactose monohydrate

Each 200 mg film-coated tablet contains 56 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

YULAREB 50 mg: oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

YULAREB 100 mg: oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

YULAREB 150 mg: oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

YULAREB 200 mg: oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Early Breast Cancer

YULAREB in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section 5.1).

In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Advanced or Metastatic Breast Cancer

YULAREB is indicated for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women; and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

  In pre- or perimenopausal women, the endocrine therapy should be combined with a Luteinising hormone-releasing hormone (LHRH) agonist.

- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

4.2. Posology and method of administration

- When used in combination with fulvestrant, tamoxifen or an aromatase inhibitor, the recommended dose of YULAREB is 150 mg taken orally twice daily. Refer to the Full Professional Information of the individual adjuvant medicines for the recommended doses.
- Pre/perimenopausal women and men treated with the combination of YULAREB plus an aromatase inhibitor should be treated with a gonadotropin-releasing hormone agonist (GnRH) according to current clinical practice standards.
- Pre/perimenopausal women treated with the combination of YULAREB plus fulvestrant should be treated with a GnRH according to current clinical practice standards.
- When used as monotherapy, the recommended dose of YULAREB is 200 mg taken orally twice daily.

Duration of treatment

Early Breast Cancer

YULAREB should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs.

Advanced or Metastatic Breast Cancer

YULAREB should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

YULAREB may be taken with or without food (see section 5.2).

If the patient vomits or misses a dose of YULAREB, instruct the patient to take the next dose at its scheduled time. Instruct patients to swallow YULAREB tablets whole and not to chew, crush, or split tablets before swallowing. Instruct patients not to ingest YULAREB tablets if broken, cracked, or otherwise not intact.

Dose Modification

Dose Modifications for Adverse Reactions

Management of some adverse events may require dose interruption and/or dose reduction. If dose reduction is necessary, decrease the dose by 50 mg at a time. Discontinue YULAREB for patients unable to tolerate 50 mg twice daily.

Table 1: YULAREB Dose Modification for Adverse events

Dose Level	**YULAREB Dose Combination with Fulvestrant, Tamoxifen, or an Aromatase Inhibitor**	**YULAREB Dose for Monotherapy**
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	Not applicable	50 mg twice daily

Table 2: YULAREB Dose Modification and Management — Haematologic Toxicities[a]

Monitor complete blood counts prior to the start of YULAREB therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE* Grade	**YULAREB Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤ Grade 2. Dose reduction is not required.
Grade 3 recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤ Grade 2. Resume at *next lower dose*.

*CTCAE = Common Terminology Criteria for adverse events.

[a] If blood cell growth factors are required, suspend YULAREB dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤ Grade 2. Resume at next lower dose unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines.

Table 3: YULAREB Dose Modification and Management - Diarrhoea

At the first sign of loose stools, start treatment with antidiarrheal medicines and increase intake of oral fluids.	
CTCAE Grade	**YULAREB Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend dose until resolution. No dose reduction is required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤ Grade 1. Resume at *next lower dose*.
Grade 3 or 4 or requires hospitalisation	Suspend dose until toxicity resolves to ≤ Grade 1. Resume at *next lower dose*.

Table 4: YULAREB Dose Modification and Management — Hepatotoxicity

Monitor ALT, AST, and serum bilirubin prior to the start of YULAREB therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade for ALT and AST	**YULAREB Dose Modifications**
Grade 1 (> ULN-3,0 x ULN) Grade 2 (> 3,0-5,0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (> 5,0-20,0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at *next lower dose*.
Elevation in AST and/or ALT > 3 x ULN WITH total bilirubin > 2 x ULN, in the absence of cholestasis	Discontinue YULAREB.
Grade 4 (> 20,0 x ULN)	Discontinue YULAREB.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

Table 5: YULAREB Dose Modification and Management - Interstitial Lung Disease/Pneumonitis

CTCAE Grade	**YULAREB Dose Modifications**
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤ Grade 1. Resume at *next lower dose*.
Grade 3 or 4	Discontinue YULAREB.

Table 6: YULAREB Dose Modification and Management — Venous Thromboembolic Events (VTEs)

CTCAE Grade	YULAREB Dose Modifications
Early Breast Cancer	
Any Grade	Suspend dose and treat as clinically indicated. Resume YULAREB when the patient is clinically stable.
Advanced or Metastatic Breast Cancer	
Grade 1 or 2	No dose modification is required.
Grade 3 or 4	Suspend dose and treat as clinically indicated. Resume YULAREB when the patient is clinically stable.

Table 7: YULAREB Dose Modification and Management for Other Toxicities[a]

CTCAE Grade	YULAREB Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4	

[a] Excluding diarrhoea, haematologic toxicity, hepatotoxicity ILD/pneumonitis and VTEs.

Refer to the Full Prescribing Information of the coadministered fulvestrant, tamoxifen, or an aromatase inhibitor for dose modifications and other relevant safety information.

Dose Modification for Use with Strong and Moderate CYP3A inhibitors

Avoid concomitant use of the strong CYP3A inhibitor ketoconazole.

With concomitant use of strong CYP3A inhibitors other than ketoconazole, in patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the YULAREB dose to 100 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the YULAREB dose to 50 mg twice daily. If a patient taking YULAREB discontinues a CYP3A inhibitor, increase the YULAREB dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor (see section 4.5).

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the YULAREB dose in 50 mg decrements as demonstrated in Table 1, if necessary.
Avoid grapefruit or grapefruit juice (see section 4.5).

Special populations

Elderly

No dose adjustment is required based on age (see section 5.2).

Renal impairment

No dose adjustments are necessary in patients with mild or moderate renal impairment. There are no data regarding abemaciclib administration in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section 5.2). YULAREB should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity.

Hepatic impairment

No dose adjustments are necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, a decrease in dosing frequency to once daily is recommended (see section 5.2).

Refer to the Full Professional Information of the coadministered fulvestrant, tamoxifen, or aromatase inhibitor or fulvestrant for dose modification requirements for severe hepatic impairment.

Paediatric population

The safety and efficacy of abemaciclib in children and adolescents aged less than 18 years has not been established.

No data are available.

4.3 Contraindications

Hypersensitivity to abemaciclib or any of the ingredients in YULAREB.

Concomitant use with ketoconazole (see section 4.5)

Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Diarrhoea

Severe diarrhoea associated with dehydration and infection occurred in patients treated with YULAREB.

Diarrhoea occurred in 81 % to 90 % of patients receiving YULAREB in clinical trials. Grade 3 diarrhoea occurred in 8 % to 20 % of these patients.

Most patients experienced diarrhoea during the first month of YULAREB treatment. The median time to onset of the first diarrhoea event ranged from 6 to 8 days and the median duration of diarrhoea for grades 2 and 3 diarrhoea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 % to 26 % of patients with diarrhoea required a YULAREB dose interruption and 13 % to 23 % required a dose reduction.

Instruct patients that at the first sign of loose stools, they should start antidiarrhoeal therapy, increase oral fluids and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhoea or diarrhoea that requires hospitalization, discontinue YULAREB until toxicity resolves to ≤ Grade 1, and then resume YULAREB at the next lower dose (see section 4.2).

Neutropenia

Neutropenia, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with YULAREB.

Neutropenia occurred in 37 % to 46 % of patients receiving YULAREB in clinical trials. A Grade ≥ 3 decrease in neutrophil count (based on laboratory findings) occurred in 19 % to 32 % of these patients. The median time to first episode of Grade ≥ 3 neutropenia ranged from 29 days to 33 days, and the median duration of Grade ≥ 3 neutropenia ranged from 11 days to 16 days.

Febrile neutropenia has been reported in < 1 % of patients exposed to YULAREB across trials.

Monitor complete blood counts prior to starting YULAREB therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2).

Interstitial Lung Disease (ILD) or Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with YULAREB and other CDK4/6 inhibitors.

Monitor patients for pulmonary symptoms indicative of ILD or pneumonitis. Symptoms may include hypoxia, cough, dyspnoea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended for patients who develop persistent or recurrent Grade 2 ILD or pneumonitis. Permanently discontinue YULAREB in all patients with Grade 3 or 4 ILD or pneumonitis (see section 4.2)

Hepatotoxicity

Grade ≥3 increased ALT (2 % to 6 %) and AST (2 % to 3 %) were reported in patients receiving YULAREB in breast cancer studies.

Across clinical trials, the median time to onset of Grade ≥ 3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade < 3 was 13 to 14 days. The median time to onset of Grade ≥ 3 AST increases ranged from 71 to 185 days and the median time to resolution to Grade < 3 ranged from 11 to 15 days.

Monitor liver function tests (LFTs) prior to the start of YULAREB therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Based on the level of ALT elevations, YULAREB may require dose modification (see section 4.2).

Venous Thromboembolism

Across clinical trials venous thromboembolic events 159 were reported in 2 % to 5 % of patients treated with YULAREB. Venous thromboembolic events including deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis have been reported. Across the clinical development program, deaths due to venous thromboembolism have been reported.

YULAREB has not been studied in patients with early breast cancer who had a history of venous thromboembolism. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for early breast cancer

patients with any grade venous thromboembolic event and for advanced or metastatic breast cancer patients with a Grade 3 or 4 venous thromboembolic event (see section 4.2).

Arterial Thromboembolic Events

A potential increased risk for serious arterial thromboembolic events (ATEs), including ischemic stroke and myocardial infarction, has been observed in metastatic breast cancer studies when YULAREB was administered in combination with endocrine therapies. The benefits and risks of continuing YULAREB in patients who experience a serious ATE should be considered.

Embryo-Foetal Toxicity

Based on findings from animal studies and the mechanism of action, YULAREB can cause foetal harm when administered to a pregnant woman (see Human reproduction, pregnancy).

Lactose

Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take YULAREB.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A inhibitors

YULAREB is primarily metabolised by CYP3A. Concomitant use of a CYP3A inhibitor, clarithromycin resulted in a 3,4-fold increase in the plasma exposure of YULAREB and a 2,2-fold increase in the plasma exposure of YULAREB plus YULAREB active metabolites in patients with advanced and/or metastatic cancer.

Ketoconazole

Do not use with ketoconazole. Ketoconazole increases the AUC of YULAREB by up to 16-fold (see section 4.3).

Other strong CYP3A inhibitors

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the YULAREB dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the YULAREB dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking YULAREB discontinues a strong CYP3A inhibitor, increase the YULAREB dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

Moderate CYP3A Inhibitors

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the YULAREB dose in 50 mg decrements as demonstrated in Table 1, if necessary.

Strong and moderate CYP3A Inducers

Concomitant use of YULAREB with the CYP3A inducer rifampicin decreased the plasma exposure of YULAREB plus its active metabolites by 95 % and 77 % respectively, based on AUC. Concomitant use of CYP3A inducers with YULAREB is not recommended (see section 4.2).

YULAREB and its major active metabolites inhibit the renal transporters organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. *In vivo* interactions of YULAREB with clinically relevant substrates of these transporters, such as creatinine, may occur (see section 4.8).

Based on the *in vitro* inhibition of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) observed with YULAREB, *in vivo* interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin, may occur.

No clinically relevant pharmacokinetic drug interactions were observed between YULAREB and anastrozole, exemastane, fulvestrant, letrozole, or tamoxifen.

4.6 Fertility, pregnancy and lactation

Pregnancy

YULAREB is contraindicated during pregnancy (see section 4.3)

Based on findings in animals, YULAREB can cause foetal harm when administered to a pregnant woman. In animal studies, YULAREB was teratogenic and caused decreased foetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the recommended human dose. Advise pregnant women of the potential risk to a foetus.

Women of childbearing potential

Women with reproductive potential should have a negative pregnancy test before starting YULAREB. They should use highly effective contraception during treatment and for 3 weeks after the last dose of YULAREB.

Breastfeeding

Women taking YULAREB should not breastfeed their infants (see section 4.3).

Because of the potential for serious adverse events in breastfeeding infants from YULAREB, a breastfeeding woman should not breastfeed during treatment with YULAREB and for at least 3 weeks after the last dose.

Fertility

Cytotoxic effects to the male reproductive tract in rats and dogs indicate that YULAREB may impair fertility in males.

No effects on female reproductive organs were observed.

4.7 Effects on ability to drive and use machines

The adverse effects of YULAREB may impair driving ability and the ability to handle machines, e.g., dizziness, diarrhoea, vomiting (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, leukopenia, anaemia, fatigue, nausea, vomiting, alopecia and decreased appetite.

Of the most common adverse reactions, Grade ≥ 3 events were less than 5 % with the exception of neutropenia, leukopenia, and diarrhoea.

Tabulated list of adverse reactions

In the following table, adverse reactions are listed in order of MedDRA body system organ class and frequency. Frequency gradings are: very common (≥ 1 / 10), common (≥ 1 / 100 to < 1 / 10), uncommon (≥ 1 / 1 000 to < 1 / 100), rare (≥ 1 / 10 000 to < 1 / 1 000), very rare (< 1 / 10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 8. Adverse reactions reported in the phase 3 studies of abemaciclib in combination with endocrine therapy[a] (N = 3 559)

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Infections [b]		
Blood and lymphatic system disorders	Neutropenia Leukopenia Anaemia Thrombocytopenia Lymphopenia [h]		Febrile neutropenia[e]
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Headache [f] Dysgeusia [g] Dizziness [g]		
Eye disorders		Lacrimation increased	
Vascular disorders		Venous thromboembolism [c]	
Respiratory, thoracic and mediastinal disorders		ILD/pneumonitis [d]	
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Stomatitis [f]	Dyspepsia [f]	
Skin and subcutaneous tissue disorders	Alopecia [g] Pruritus [g] Rash [g]	Nail disorder [f] Dry skin [e]	
Musculoskeletal and connective tissue disorders		Muscular weakness [e]	
General disorders and administration site conditions	Pyrexia [e] Fatigue		
Investigations	Alanine aminotransferase increased [g]		
	Aspartate aminotransferase increased [g]		

[a] Abemaciclib in combination with anastrozole, letrozole, exemestane, tamoxifen, or fulvestrant.

[b] Infections include all reported Preferred Terms that are part of the System Organ Class Infections and Infestations.

[c] Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral

venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis.

[d] Interstitial lung disease (ILD)/pneumonitis for early breast cancer (EBC) include all reported Preferred Terms that are part of the MedDRA SMQ interstitial lung disease. For metastatic breast cancer (mBC) Preferred Terms include interstitial lung disease, pneumonitis, organising pneumonia, pulmonary fibrosis and bronchiolitis obliterans.

[e] Considered ADRs in the mBC setting only (MONARCH 2 and MONARCH 3).

[f] Considered ADRs in the EBC setting only (monarchE).

[g] Common frequency in the EBC setting (monarchE), very common in the mBC setting (MONARCH 2 and MONARCH 3).

[h] Common frequency in mBC setting (MONARCH 2 and MONARCH 3), very common in the EBC setting (monarchE).

Diarrhoea

Diarrhoea was the most commonly reported adverse reaction (see table 8). Diarrhoea incidence was greatest during the first month of YULAREB dosing and was lower during subsequent months. Patients recovered to baseline or lesser grade diarrhoea with supportive treatment, such as loperamide, and/or dose reductions (see section 4.2).

Neutropenia

Neutropenia was reported frequently across studies. In the monarchE study, neutropenia was reported in 45,8 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 19,1 % of patients receiving abemaciclib in combination with endocrine therapy with a median time to onset of 30 days, and median time to resolution of 16 days. Febrile neutropenia was reported in 0,3 % patients. In MONARCH 2 and MONARCH 3 studies, neutropenia was reported in 45,1 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28,2 % of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile neutropenia was reported

in 0,9 % patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2).

Increased aminotransferases

In the monarchE study, ALT and AST elevations were reported frequently (12,3 % and 11,8 %, respectively) in patients receiving abemaciclib in combination with endocrine therapy. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 2,6 % and 1,6 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 118 days, and median time to resolution was 14,5 days. The median time to onset of Grade 3 or 4 AST elevation was 90,5 days, and median time to resolution was 11 days. In MONARCH 2 and MONARCH 3 studies, ALT and AST elevations were reported frequently (15,1 % and 14,2 %, respectively) in patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6,1 % and 4,2 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2).

Increased Serum Creatinine

YULAREB has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). Increases in serum creatinine occurred within the first month of YULAREB dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation, and the increase is not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Adverse reactions from spontaneous reporting

The following adverse reactions have been identified during post-approval use of YULAREB. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory disorders: Interstitial lung disease (ILD)/pneumonitis (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

Alternately, report suspected adverse events to the company at ade_za@lilly.com.

4.9. Overdose

In case of overdose, use supportive therapy. There is no known antidote for YULAREB overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinases inhibitors, ATC code: L01XE50

Mechanism of action

Abemaciclib is an inhibitor of cyclin D-dependent kinases 4 and 6 (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 into S phase of the cell cycle, leading to suppression of tumour growth. In oestrogen receptor–positive breast cancer cell lines, sustained target inhibition by abemaciclib prevents rebound of Rb phosphorylation and cell cycle re-entry, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations as a single medicine or in combination with antioestrogens resulted in reduction of tumour size.

Cardiac Electrophysiology

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (i.e., 20 ms) in the QTc interval.

Clinical efficacy and safety

Randomised Phase 3 Study monarchE: Abemaciclib in combination with endocrine therapy

The efficacy and safety of Abemaciclib in combination with adjuvant endocrine therapy was evaluated in monarchE, a randomised, open label, two cohort, phase 3 study, in women and men with HR-positive, HER2-negative, node positive early breast cancer at high risk of recurrence. High risk of recurrence in Cohort 1 was defined by clinical and pathological features: either ≥ 4 pALN (positive axillary lymph nodes), or 1-3 pALN and at least one of the following criteria: tumor size ≥ 5 cm or histological grade 3.

A total of 5 637 patients were randomised in a 1:1 ratio to receive 2 years of abemaciclib 150 mg twice daily plus physician’s choice of standard endocrine therapy, or standard endocrine therapy alone. Randomization was stratified by prior chemotherapy, menopausal status, and region. Men

were stratified as postmenopausal. Patients had completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy). Patients must have recovered from the acute side effects of any prior chemotherapy or radiotherapy. A washout period of 21 days after chemotherapy and 14 days after radiotherapy prior to randomization was required. Patients were allowed to receive up to 12 weeks of adjuvant endocrine therapy prior to randomisation. Adjuvant treatment with fulvestrant was not allowed as standard endocrine therapy. Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 were eligible. Patients with history of VTEs were excluded from the study. After the end of the study treatment period, in both treatment arms patients continued to receive adjuvant endocrine therapy for a cumulative duration of at least 5 years and up to 10 years, if medically appropriate. LHRH agonists were given when clinically indicated to pre- and perimenopausal women, and men.

Among the 5 637 randomised patients, 5 120 were enrolled in Cohort 1, representing 91 % of the ITT population. In Cohort 1, patient demographics and baseline tumour characteristics were balanced between treatment arms. The median age of patients enrolled was approximately 51 years (range, 22-89 years), 15 % of patients were 65 or older, 99 % were women, 71 % were Caucasian, 24 % were Asian, and 5 % Other. Forty three percent of patients were pre- or perimenopausal. Most patients received prior chemotherapy (36 % neoadjuvant, 62 % adjuvant), and prior radiotherapy (96 %). Initial endocrine therapy received by patients included letrozole (39 %), tamoxifen (31 %), anastrozole (22 %), or exemestane (8 %).

Sixty-five percent of the patients had 4 or more positive lymph nodes, 41 % had Grade 3 tumour, and 24 % had pathological tumour size ≥ 5 cm at surgery.

The primary endpoint was invasive disease-free survival (IDFS) in ITT population defined as the time from randomization to the first occurrence of ipsilateral invasive breast tumour recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second

primary non-breast invasive cancer, or death attributable to any cause. Key secondary endpoint was distant relapse free survival (DRFS) in ITT population defined as time from randomization to the first occurrence of distant recurrence, or death attributable to any cause.

A statistically significant improvement in IDFS was observed in patients who received abemaciclib plus endocrine therapy versus endocrine therapy alone in the ITT population.

Efficacy results in Cohort 1 are summarised in Table 9.

Table 9. monarchE: Summary of efficacy data (Cohort 1 population)

	Abemaciclib plus endocrine therapy N = 2 555	**Endocrine therapy alone N = 2 565**
Invasive disease-free survival (IDFS)		
Number of patients with event (n, %)	218 (8,5)	318 (12,4)
Hazard ratio (95 % CI)	0.680 (0.572, 0.808)	
IDFS at 24 months (%, 95 % CI)	92,6 (91,4, 93,5)	89,6 (88,3, 90,8)
Distant relapse free survival (DRFS)		
Number of patients with an event (n, %)	179 (7,0)	266 (10,4)
Hazard ratio (95 % CI)	0,669 (0,554, 0,809)	
DRFS at 24 months (%, 95 % CI)	94,1 (93,0, 95,0)	91,2 (90,0, 92.3)

Abbreviation: CI = confidence interval.

Advanced or Metastatic Breast Cancer

Three global clinical studies provide primary efficacy and safety data supporting abemaciclib used in combination with endocrine therapies and as a single medicine:

- MONARCH 3 (I3Y-MC-JPBM) — a Phase 3, multicenter, randomised, double-blind, placebo-controlled study evaluating abemaciclib in combination with a nonsteroidal aromatase inhibitor (NSAI).
- MONARCH 2 (I3Y-MC-JPBL) — a Phase 3, multicenter, randomised, double-blind, placebo-controlled study evaluating abemaciclib in combination with fulvestrant.
- MONARCH 1 (I3Y-MC-JPBN) — a Phase 2, multicenter, nonrandomised, open-label study evaluating abemaciclib as a single medicine.

Abemaciclib showed clinical benefit in patients who have not received prior systemic therapy for metastatic disease, whose disease has progressed on or after endocrine therapy, and in patients who have already received cytotoxic chemotherapy.
Overall safety profile of the 3 studies was generally consistent in terms of adverse event incidence and severity. In MONARCH 3 and MONARCH 2, the incidence for increased ALT, increased AST and decreased neutrophil count were higher in Asian patients.

5.2 Pharmacokinetic properties

Absorption

Abemaciclib absorption is slow, with a median T_{max} of 8 hours. The absolute bioavailability of abemaciclib is 45 % (90 % confidence interval: 40-51 %). In the therapeutic dose range of 50-200 mg, the increase in plasma exposure (AUC) and C_{max} is dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and abemaciclib accumulated with a geometric mean accumulation ratio of 3,7 (58 % CV) and 5,8 (65 % CV) based on C_{max} and AUC, respectively.
Administration with meals is not associated with a clinically relevant effect on exposure. Abemaciclib may be administered with or without food.

Distribution

In vitro, abemaciclib was highly bound to plasma proteins in humans (mean bound fraction was approximately 96-98 %), and the binding was independent of concentration from 152 ng/ml to 5 066 ng/ml. Abemaciclib binds to both human serum albumin and alpha-1-acid glycoprotein. The geometric mean systemic volume of distribution is approximately 747 L (68,6 % CV).
In patients with advanced cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.

Metabolism

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolised to several metabolites primarily by cytochrome P450 (CYP) 3A, with formation of N-desethyl abemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). Metabolites N-desethylabemaciclib (M2) and hydroxyabemaciclib (M20) are active with similar potency as abemaciclib.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib was 21,8 L/h (39,8 % CV), and the mean plasma elimination half-life for abemaciclib in patients was 24,8 hours (52,1 % CV). After a single oral dose of [14C]-abemaciclib, approximately 81 % of the dose was excreted in faeces and 3,4 % excreted in urine. The majority of the dose eliminated in faeces was metabolites.

Special Populations

Age, sex, and body weight had no effect on the exposure of abemaciclib in a population pharmacokinetic analysis in patients with cancer (135 males and 859 females; age range 24-91 years; and body weight range 36-175 kg).

Hepatic impairment: Abemaciclib is metabolised in the liver. Mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had no effect on the exposure of abemaciclib. In subjects with severe

hepatic impairment (Child Pugh C), the $AUC_{0-\infty}$ of abemaciclib and potency adjusted unbound abemaciclib plus its active metabolites increased 2,1-fold and 2,4-fold, respectively and the abemaciclib half-life increased from 24 to 55 hours. Reduce the abemaciclib dosing frequency to once daily in patients with severe hepatic impairment (see section 4.2).

Renal impairment: Abemaciclib and its metabolites are not significantly cleared renally. Dose adjustment is not necessary in patients with mild or moderate renal impairment. There are no data in patients with severe renal impairment, end stage renal disease, or in patients on dialysis.

5.3 Preclinical safety data

Genotoxicity

Abemaciclib and its active human metabolites M2 and M20 were not mutagenic in a bacterial reverse mutation (Ames) assay or clastogenic in an in vitro chromosomal aberration assay in Chinese hamster ovary cells or human peripheral blood lymphocytes. Abemaciclib, M2, and M20 were not clastogenic in an in vivo rat bone marrow micronucleus assay.

Carcinogenicity

Abemaciclib was assessed for carcinogenicity in a 2-year rat study. Abemaciclib was not carcinogenic in male and female rats at oral doses up to 3 mg/kg/day (approximately 1 time the exposure at the maximum recommended human dose based on AUC).

Impairment of fertility

Abemaciclib may impair fertility in males of reproductive potential. In repeat-dose toxicity studies up to 3-months duration, abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle at doses ≥10 mg/kg/day in rats and ≥ 0,3 mg/kg/day in dogs included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These doses in rats and dogs resulted in approximately 2 and 0,02 times, respectively, the exposure (AUC) in

humans at the maximum recommended human dose. In a rat male fertility study, abemaciclib had no effects on mating and fertility at oral doses up to 10 mg/kg/day (approximately 2 times the exposure at the maximum recommended human dose based on AUC).

In a rat female fertility and early embryonic development study, abemaciclib did not affect mating and fertility at doses up to 20 mg/kg/day (approximately 3 times the exposure at the maximum recommended human dose based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- croscarmellose sodium
- lactose monohydrate
- microcrystalline cellulose 101
- microcrystalline cellulose 102
- silica, colloidal hydrated
- sodium stearyl fumarate

Colour Mixture Beige Ingredients (50 mg and 200 mg tablets):

- polyvinyl alcohol [E1203]
- titanium dioxide [E171]
- polyethylene glycol or macrogol [polyethylene glycol MW 3350 or macrogol 4000] [E1521]
- talc [E553b]
- iron oxide yellow [E172]
- iron oxide red [E172]

Colour Mixture White Ingredients (100 mg tablet):

- polyvinyl alcohol [E1203]

- titanium dioxide [E171]
- polyethylene glycol or macrogol [polyethylene glycol MW 3350 or macrogol 4000] [E1521]
- talc [E553b]

Colour Mixture Yellow Ingredients (150 mg tablet):

- polyvinyl alcohol [E1203]
- titanium dioxide [E171]
- polyethylene glycol or macrogol [polyethylene glycol MW 3350 or macrogol 4000] [E1521]
- talc [E553b]
- iron oxide yellow [E172]

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

YULAREB tablets are supplied in a cold form aluminium foil (CFAF) blister with aluminium foil lidding, packaged in an outer carton in packs of 14 or 28 tablets per pack. Not all pack sizes may be marketed.

YULAREB 50 mg: oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

YULAREB 100 mg: oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

YULAREB 150 mg: oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

YULAREB 200 mg: oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston, 2191

8. REGISTRATION NUMBER(S)

YULAREB 50 mg: 53/26/0438.434

YULAREB 100 mg: 53/26/0439.435

YULAREB 150 mg: 53/26/0440.436

YULAREB 200 mg: 53/26/0441.437

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 December 2020

10. DATE OF REVISION OF THE TEXT

28 October 2024

Manufactured by:

Lilly del Caribe, Inc.

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Carolina, Puerto Rico (PR) 00985

USA

Packaged by:

Lilly, S.A.

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28108 Alcobendas, Madrid

Spain

PATIENT COUNSELLING INFORMATION

Advise patients to read the approved Patient Information Leaflet.

Diarrhoea

YULAREB may cause diarrhoea, which may be severe in some cases.

- Early identification and intervention are critical for the optimal management of diarrhoea. Instruct patients that at the first sign of loose stools, they should start antidiarrhoeal therapy and notify their healthcare provider for further instructions and appropriate follow up.
- Encourage patients to increase oral fluids.
- If diarrhoea does not resolve with antidiarrhoeal therapy within 24 hours to ≤ Grade 1, suspend YULAREB dosing.

Neutropenia

Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection.

Hepatotoxicity

Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity.

Venous Thromboembolism

Advise patients to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnea, and tachycardia.

Embryo-Foetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a foetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

- Advise females of reproductive potential to use effective contraception during YULAREB treatment and for 3 weeks after the last dose.

Lactation

Advise lactating women not to breastfeed during YULAREB treatment and for at least 3 weeks after the last dose.

Infertility

Inform males of reproductive potential that YULAREB may impair fertility.

Medicines Interactions

- Inform patients to avoid concomitant use of ketoconazole. Dose reduction may be required for other strong CYP3A inhibitors.
- Grapefruit may interact with YULAREB. Advise patients not to consume grapefruit products while on treatment with YULAREB.
- Advise patients to avoid concomitant use of CYP3A inducers and to consider alternative medicines.
- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

Dosing

- Instruct patients to take the doses of YULAREB at approximately the same times every day and to swallow whole (do not chew, crush, or split them prior to swallowing). If patient vomits or misses a dose, advise the patient to take the next prescribed dose at the usual time.
- Advise the patient that YULAREB may be taken with or without food.