1. NAME OF THE MEDICINAL PRODUCT

1.1 Product name:

YULAREB™ (abemaciclib)

1.2 Strength:

- YULAREB 50 mg film-coated tablets
- YULAREB 100 mg film-coated tablets
- YULAREB 150 mg film-coated tablets
- YULAREB 200 mg film-coated tablets

1.3 Pharmaceutical dosage form: Film-coated tablet (tablet).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

For oral use. Oval, film-coated tablet

- 50 mg tablets: oval beige tablet with “Lilly” debossed on one side and “50” on the other side.
- 100 mg tablets: oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.
- 150 mg tablets: oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.
- 200 mg tablets: oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YULAREB® (abemaciclib) is indicated:

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women 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 women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- 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 or an aromatase inhibitor, the recommended dose of YULAREB is 150 mg taken orally twice daily.

- When given with YULAREB, refer to the Full Prescribing Information for the recommended dose of the aromatase inhibitor being used.
- When given with YULAREB, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29; and once monthly thereafter. Refer to the Full Prescribing Information for fulvestrant. Pre/perimenopausal women treated with the combination of YULAREB plus fulvestrant should be treated with a gonadotropin-releasing hormone agonist according to current clinical practice standards.

When used as monotherapy, the recommended dose of YULAREB is 200 mg taken orally twice daily.

Continue treatment until disease progression or unacceptable toxicity. YULAREB may be taken with or without food [*see Pharmacokinetic properties (5.2)*].

Instruct patients to take their doses of YULAREB at approximately the same times every day.

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 Modifications for Adverse Reactions

The recommended YULAREB dose modifications for adverse reactions are provided in Tables 1-6. Discontinue YULAREB for patients unable to tolerate 50 mg twice daily.

Table 1: YULAREB Dose Modification for Adverse Reactions

Dose Level	YULAREB Dose Combination with Fulvestrant 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 — Hematologic 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*.

Abbreviation: 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 — Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents 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 hospitalization	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 for 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 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	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.

[a] Excluding diarrhea, hematologic toxicity, hepatotoxicity, and ILD/pneumonitis.

Refer to the Full Prescribing Information for coadministered aromatase inhibitor or fulvestrant 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 Interaction with other medicinal products and other forms of interaction (4.5) and Pharmacokinetic properties (5.2)]*.

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.

Dose Modification for Patients with Severe Hepatic Impairment

*For patients with severe hepatic impairment (Child Pugh-C), reduce the YULAREB dosing frequency to once daily [see Special warnings and precautions for use (4.4) and Pharmacokinetic properties (*5.2*)].*

Refer to the Full Prescribing Information for coadministered aromatase inhibitor or fulvestrant for dose modification requirements for severe hepatic impairment.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

4.4.1 Diarrhea

Diarrhea occurred in 81% of patients receiving YULAREB plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving YULAREB plus fulvestrant in MONARCH 2, and 90% of patients receiving YULAREB alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving YULAREB plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving YULAREB plus fulvestrant in MONARCH 2, and in 20% of patients receiving YULAREB alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of YULAREB dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively *[see Posology and method of administration (4.2)*]. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue YULAREB until toxicity resolves to ≤Grade 1, and then resume YULAREB at the next lower dose *[see Posology and method of administration (4.2)*].

4.4.2 Neutropenia

Neutropenia occurred in 41% of patients receiving YULAREB plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving YULAREB plus fulvestrant in MONARCH 2, and 37% of patients receiving YULAREB alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving YULAREB plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving YULAREB plus fulvestrant in MONARCH 2, and in 27% of patients receiving YULAREB in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days *[see Undesirable effects (4.8)]*.

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. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia *[see Posology and method of administration (4.2)*].

Febrile neutropenia has been reported in <1% of patients exposed to YULAREB in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

4.4.3 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with YULAREB and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of YULAREB-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported *[see Undesirable effects (4.8)].*

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, 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/pneumonitis. Permanently discontinue YULAREB in all patients with Grade 3 or 4 ILD or pneumonitis *[see Posology and method of administration (4.2)].*

4.4.4 Hepatotoxicity

In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the YULAREB and placebo arms, respectively. In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the YULAREB and placebo arms, respectively.

In MONARCH 3, for patients receiving YULAREB plus an aromatase inhibitor with Grade ≥3 ALT increased, median time to onset was 61 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 2, for patients receiving YULAREB plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 3, for patients receiving YULAREB plus an aromatase inhibitor with Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving YULAREB plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 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. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation *[see Posology and method of administration (4.2)].*

4.4.5 Venous Thromboembolism

In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with YULAREB plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with YULAREB plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

4.4.6 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, YULAREB can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with YULAREB and for at least 3 weeks after the last dose *[see Fertility, pregnancy and lactation (4.6.1, 4.6.3) and Pharmacological Properties (5)]*.

4.4.7 Pediatric Use

The safety and effectiveness of YULAREB have not been established in pediatric patients.

4.4.9 Geriatric Use

Of the 900 patients who received YULAREB in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT

increased. No overall differences in safety or effectiveness of YULAREB were observed between these patients and younger patients.

4.4.10 Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown [*see Pharmacokinetic properties (5.2)*].

4.4.11 Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Reduce the dosing frequency when administering YULAREB to patients with severe hepatic impairment (Child-Pugh C) [see *Posology and method of administration (4.2)* and *Pharmacokinetic properties (5.2)*].

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Other Drugs on YULAREB

CYP3A Inhibitors

Strong and moderate CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold *[see Pharmacokinetic properties (5.2)*].

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. Patients should avoid grapefruit products [see *Posology and method of administration (4.2)* and *Pharmacokinetic properties (5.2)*].

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

Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents *[see Pharmacokinetic properties (5.2)*].

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, YULAREB can cause fetal harm when administered to a pregnant woman *[see Pharmacological Properties (5)]*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose [*see Pharmacological Properties (5)]*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

4.6.2 Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from YULAREB, advise lactating women not to breastfeed during YULAREB treatment and for at least 3 weeks after the last dose.

4.6.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, YULAREB can cause fetal harm when administered to a pregnant woman *[see Fertility, pregnancy and lactation (4.6)]*. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with YULAREB.

Contraception

Females

YULAREB can cause fetal harm when administered to a pregnant woman *[see Fertility, pregnancy and lactation (4.6)]*. Advise females of reproductive potential to use effective contraception during YULAREB treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, YULAREB may impair fertility in males of reproductive potential *[see Preclinical safety data (5.3)]*.

4.7 Effects on ability to drive and use machines

No studies have been conducted to determine the effects of abemaciclib on the ability to drive or use machines.

4.8 Undesirable effects

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Diarrhea *[see Special warnings and precautions for use (4.4)]*.
- Neutropenia *[see Special warnings and precautions for use (4.4)]*.
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Special warnings and precautions for use (4.4)]*.
- Hepatotoxicity *[see Special warnings and precautions for use (4.4)]*.
- Venous Thromboembolism *[see Special warnings and precautions for use (4.4)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

MONARCH 3: YULAREB in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy

Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3 was a study of 488 women receiving YULAREB plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of YULAREB or placebo orally twice daily, plus physician's choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the YULAREB arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the YULAREB arm and 99% for the placebo arm.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving YULAREB plus anastrozole or letrozole. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. YULAREB dose reductions due to diarrhea of any grade occurred in 13% of patients receiving YULAREB plus an aromatase inhibitor compared to 2% of patients receiving placebo plus an aromatase inhibitor. YULAREB dose reductions due to neutropenia of any grade occurred in 11% of patients receiving YULAREB plus an aromatase inhibitor compared to 0.6% of patients receiving placebo plus an aromatase inhibitor.

Permanent treatment discontinuation due to an adverse event was reported in 13% of patients receiving YULAREB plus an aromatase inhibitor and in 3% of patients receiving placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving YULAREB plus an aromatase inhibitor were diarrhea (2%), ALT increased (2%), infection (1%), venous thromboembolic events (VTE) (1%), neutropenia (0.9%), renal impairment (0.9%), AST increased (0.6%), dyspnea (0.6%), pulmonary fibrosis (0.6%) and anemia, rash, weight decreased and thrombocytopenia (each 0.3%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 11 cases (3%) of YULAREB plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving YULAREB plus an aromatase inhibitor included: 3 (0.9%) patient deaths due to underlying disease, 3 (0.9%) due to lung infection, 3 (0.9%) due to VTE event, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the YULAREB arm and ≥2% than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leukopenia (Table 7). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia. Diarrhea incidence was greatest during the first month of YULAREB dosing. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grades 2 and for Grade 3 were 11 days and 8 days, respectively. Most diarrhea events recovered or resolved (88%) with supportive treatment and/or dose reductions [see *Posology and method of administration (4.2)*]. Nineteen percent of patients with diarrhea required a dose omission and 13% required a dose reduction. The median time to the first dose reduction due to diarrhea was 38 days.

Table 7: Adverse Reactions ≥10% of Patients Receiving YULAREB Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	YULAREB plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	81	9	0	30	1	0
Nausea	39	<1	0	20	1	0
Abdominal pain	29	1	0	12	1	0
Vomiting	28	1	0	12	2	0
Constipation	16	<1	0	12	0	0
Infections and Infestations						
Infections[a]	39	4	<1	29	2	<1
Blood and Lymphatic System Disorders						
Neutropenia	41	20	2	2	<1	<1
Anemia	28	6	0	5	1	0
Leukopenia	21	7	<1	2	0	<1
Thrombocytopenia	10	2	<1	2	<1	0
General Disorders and Administration Site Conditions						
Fatigue	40	2	0	32	0	0
Influenza like illness	10	0	0	8	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	27	0	0	11	0	0
Rash	14	<1	0	5	0	0
Pruritus	13	0	0	9	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	24	1	0	9	<1	0
Investigations						
Blood creatinine increased	19	2	0	4	0	0
Alanine aminotransferase increased	16	6	<1	7	2	0
Aspartate aminotransferase increased	15	3	0	7	1	0
Weight decreased	10	<1	0	3	<1	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	9	0	0
Dyspnea	12	<1	<1	6	<1	0
Nervous System Disorders						
Dizziness	11	<1	0	9	0	0

[a] Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>1%) include upper respiratory tract infection, lung infection, and pharyngitis.

Additional adverse reactions in MONARCH 3 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, and pelvic venous thrombosis), which were reported in 5% of patients treated with YULAREB plus anastrozole or letrozole as compared to 0.6% of patients treated with anastrozole or letrozole plus placebo.

Table 8: Laboratory Abnormalities ≥10% in Patients Receiving YULAREB Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	YULAREB plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	2	0	84	0	0
White blood cell decreased	82	13	0	27	<1	0
Anemia	82	2	0	28	0	0
Neutrophil count decreased	80	19	3	21	3	0
Lymphocyte count decreased	53	7	<1	26	2	0
Platelet count decreased	36	1	<1	12	<1	0
Alanine aminotransferase increased	48	6	<1	25	2	0
Aspartate aminotransferase increased	37	4	0	23	<1	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function *[see Pharmacokinetic properties (5.2)]*. Across the clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of YULAREB dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

MONARCH 2: YULAREB in Combination with Fulvestrant

Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of YULAREB (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to YULAREB in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of YULAREB plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving YULAREB plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving YULAREB plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. YULAREB dose reductions due to diarrhea of any grade occurred in 19% of patients receiving YULAREB plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. YULAREB dose reductions due to neutropenia of any grade occurred in 10% of patients receiving YULAREB plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event were reported in 9% of patients receiving YULAREB plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving YULAREB plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of YULAREB plus fulvestrant treated patients versus 10 cases (5%) of placebo plus

fulvestrant treated patients. Causes of death for patients receiving YULAREB plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the YULAREB arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 9). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 9: Adverse Reactions ≥10% in Patients Receiving YULAREB Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	YULAREB plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0

Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.

[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

[c] Includes neutropenia, neutrophil count decreased.

[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[e] Includes leukopenia, white blood cell count decreased.

[f] Includes platelet count decreased, thrombocytopenia.

[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with YULAREB plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 10: Laboratory Abnormalities ≥10% in Patients Receiving YULAREB Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	YULAREB plus Fulvestrant N=441			**Placebo plus Fulvestrant N=223**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function *[see Pharmacokinetic properties (5.2)]*. In clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of YULAREB dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

YULAREB Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg YULAREB orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths due to adverse events during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection (2 patients) or pneumonitis (1 patient).

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 11). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib [see *Posology and method of administration (4.2)*].

Table 11: Adverse Reactions (≥10% of Patients) in MONARCH 1

	YULAREB N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0

Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.

[b] Includes neutropenia, neutrophil count decreased.

[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[d] Includes platelet count decreased, thrombocytopenia.

[e] Includes leukopenia, white blood cell count decreased.

Table 12: Laboratory Abnormalities for Patients Receiving YULAREB in MONARCH 1

	YULAREB N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function *[see Pharmacokinetic properties (5.2)]*. In clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of YULAREB dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

Postmarketing Experience

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 Special warnings and precautions for use (4.4)]*.

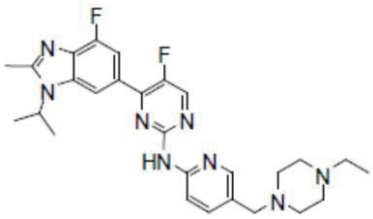
4.9 Overdose

There is no known antidote for YULAREB. The treatment of overdose of YULAREB should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

Abemaciclib is a kinase inhibitor for oral administration. It is a white to yellow powder with the empirical formula $C_{27}H_{32}F_2N_8$ and a molecular weight 506.59.

The chemical name for abemaciclib is 2-Pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1*H*-benzimidazol-6-yl]-. Abemaciclib has the following structure:



Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

5.1 Pharmacodynamic properties

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 STUDIES

YULAREB in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) (MONARCH 3)

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3 was a randomized (2:1), double-blinded, placebo-controlled, multicenter study in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer.

Randomization was stratified by disease site (visceral, bone only, or other) and by prior (neo)adjuvant endocrine therapy (aromatase inhibitor versus other versus no prior endocrine therapy). A total of 493

patients were randomized to receive 150 mg YULAREB or placebo orally twice daily, plus physician's choice of letrozole (80% of patients) or anastrozole (20% of patients). Patient median age was 63 years (range, 32-88 years) and the majority were White (58%) or Asian (30%). A total of 51% had received prior systemic therapy and 39% of patients had received chemotherapy, 53% had visceral disease, and 22% had bone-only disease.

Efficacy results are summarized in Table 13 and Figure 1. PFS was evaluated according to RECIST version 1.1 and PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across patient stratification subgroups of disease site and prior (neo)adjuvant endocrine therapy. At the time of the PFS analysis, 19% of patients had died, and overall survival data were immature.

Table 13: Efficacy Results in MONARCH 3 (Investigator Assessment, Intent-to-Treat Population)

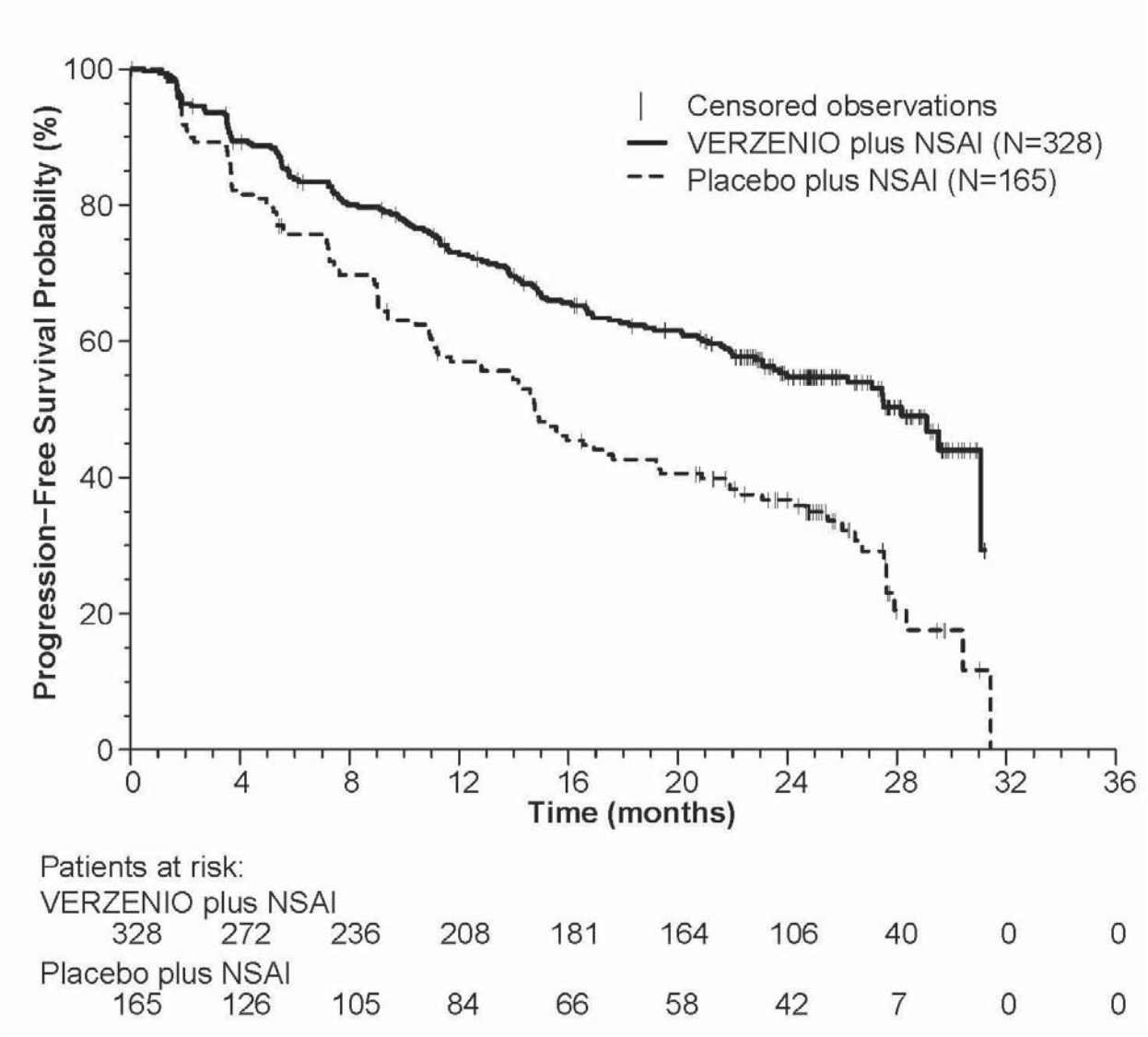
	YULAREB plus Anastrozole or Letrozole	**Placebo plus Anastrozole or Letrozole**
Progression-Free Survival	**N=328**	**N=165**
Number of patients with an event (n, %)	138 (42.1)	108 (65.5)
Median (months, 95% CI)	28.2 (23.5, NR)	14.8 (11.2, 19.2)
Hazard ratio (95% CI)	0.540 (0.418, 0.698)	
p-value	<0.0001	
Objective Response for Patients with Measurable Disease	**N=267**	**N=132**
Objective response rate[a,b] (n, %)	148 (55.4)	53 (40.2)
95% CI	49.5, 61.4	31.8, 48.5

Abbreviations: CI = confidence interval, NR = not reached.

[a] Complete response + partial response.

[b] Based upon confirmed responses.

Figure 1: Kaplan-Meier Curves of Progression-Free Survival: YULAREB plus Anastrozole or Letrozole versus Placebo plus Anastrozole or Letrozole (MONARCH 3)



YULAREB in Combination with Fulvestrant (MONARCH 2)

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. Randomization was stratified by disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance). Primary endocrine therapy resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy or progressive disease within the first 6 months of first line endocrine therapy for metastatic breast cancer. A total of 669 patients were randomized to receive YULAREB or placebo orally twice daily plus intramuscular injection of 500 mg fulvestrant on days 1 and 15 of cycle 1 and then on day 1 of cycle 2 and beyond (28-day cycles). Pre/perimenopausal women were enrolled in the study and received the gonadotropin-releasing hormone agonist goserelin for at least 4 weeks prior to and for the duration of MONARCH 2. Patients remained on continuous treatment until development of progressive disease or unmanageable toxicity.

Patient median age was 60 years (range, 32-91 years), and 37% of patients were older than 65. The majority were White (56%), and 99% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Twenty percent (20%) of patients had de novo metastatic disease, 27% had bone-only disease, and 56% had visceral disease. Twenty-five percent (25%) of patients had primary endocrine therapy resistance. Seventeen percent (17%) of patients were pre- or perimenopausal.

The efficacy results from the MONARCH 2 study are summarized in Table 14, Figure 2, and Figure 3. PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across patient stratification subgroups of disease site and endocrine therapy resistance for PFS and OS.

Table 14: Efficacy Results in MONARCH 2 (Intent-to-Treat Population)

	YULAREB plus Fulvestrant	**Placebo plus Fulvestrant**
Progression-Free Survival (Investigator Assessment)	**N=446**	**N=223**
Number of patients with an event (n, %)	222 (49.8)	157 (70.4)
Median (months, 95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI)[a]	0.553 (0.449, 0.681)	
p-value[a]	p<.0001	
Overall Survival[b]		
Number of deaths (n, %)	211 (47.3)	127 (57.0)
Median OS in months (95% CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95% CI)[a]	0.757 (0.606, 0.945)	
p-value[a]	p=.0137	
Objective Response for Patients with Measurable Disease	**N=318**	**N=164**
Objective response rate[c] (n, %)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6

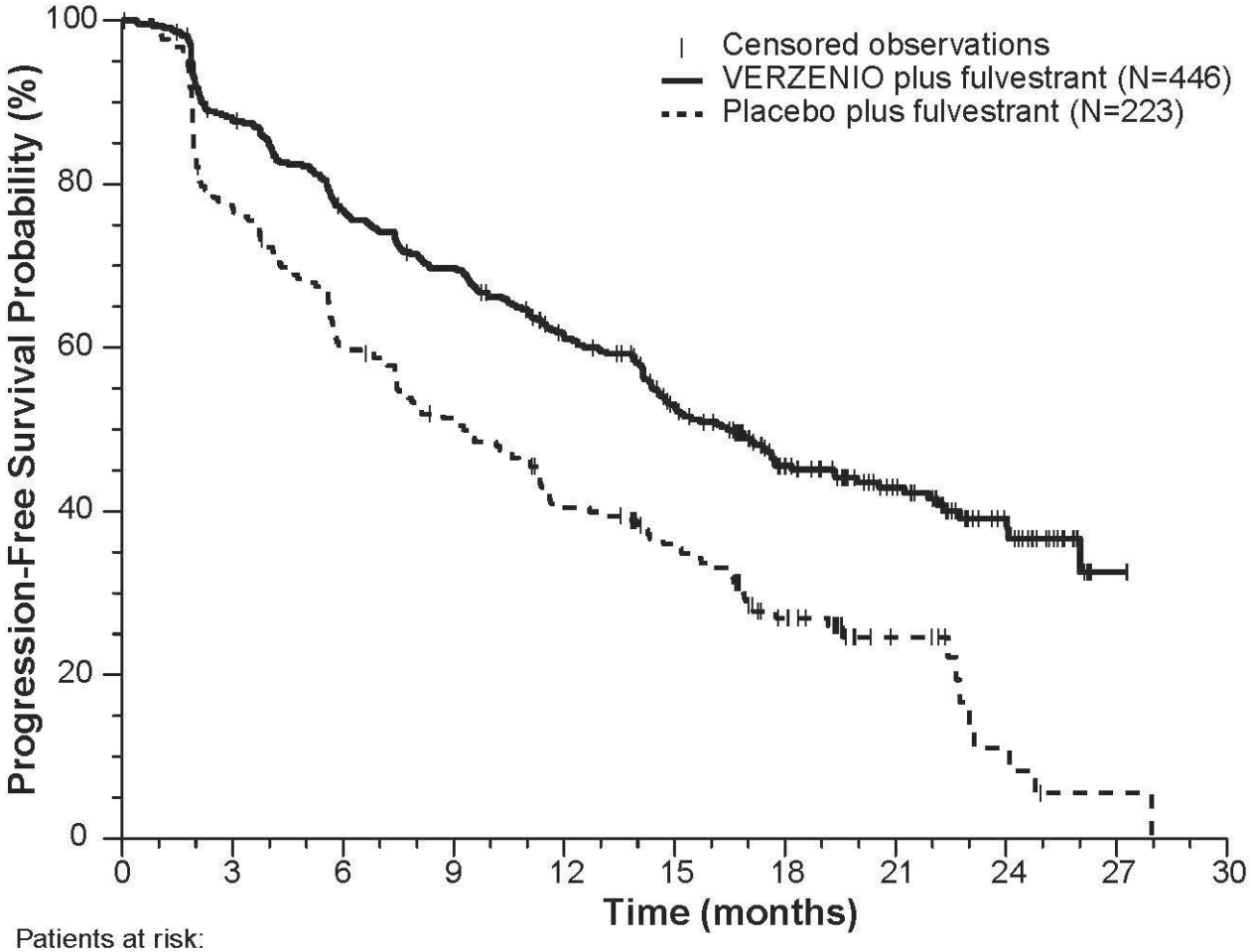
Abbreviation: CI = confidence interval, OS = overall survival.

[a] Stratified by disease site (visceral metastases vs. bone-only metastases vs. other) and endocrine therapy resistance (primary resistance vs. secondary resistance)

[b] Data from a pre-specified interim analysis (77% of the number of events needed for the planned final analysis) with the p-value compared with the allocated alpha of 0.021.

[c] Complete response + partial response.

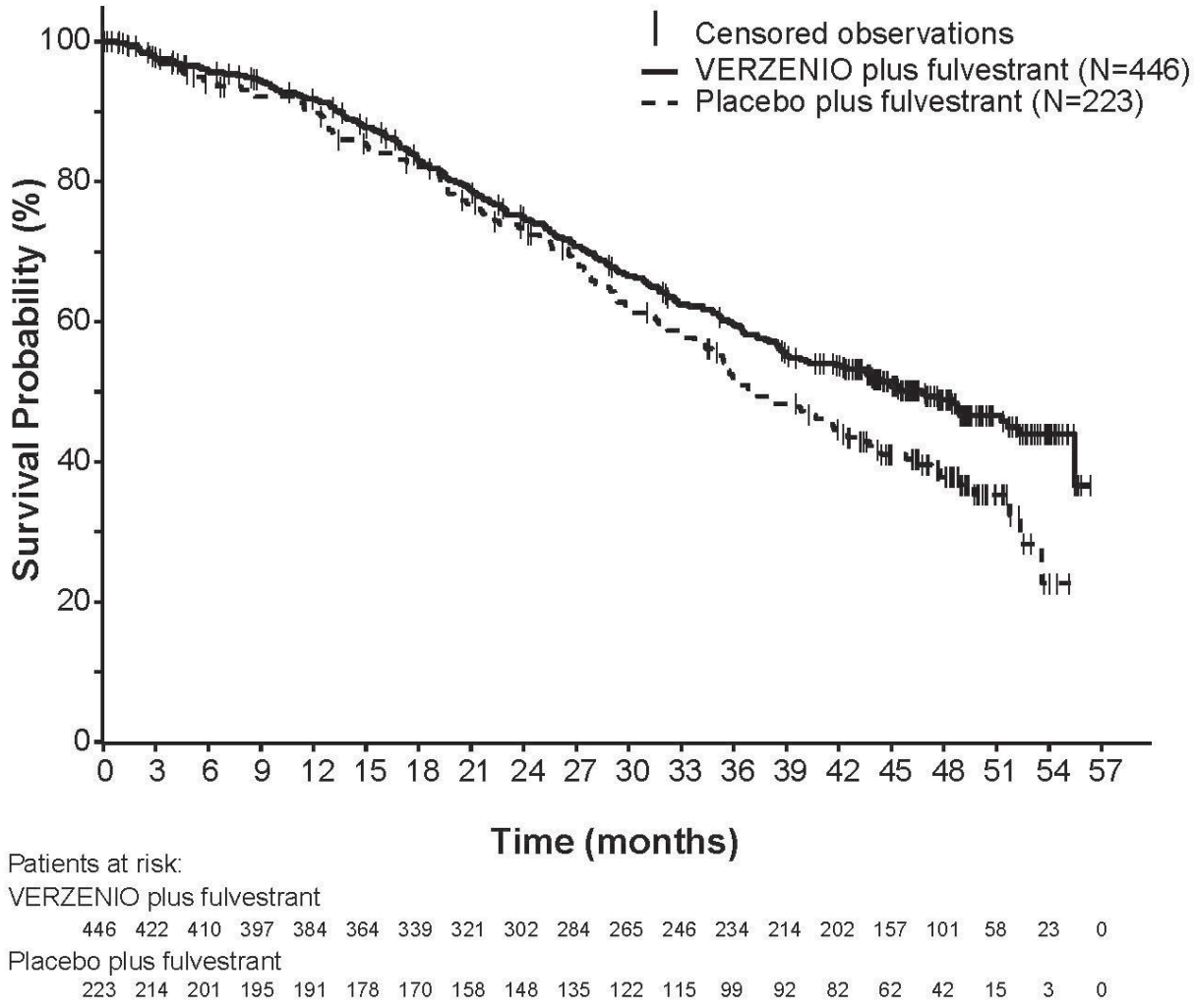
Figure 2: Kaplan-Meier Curves of Progression-Free Survival: YULAREB plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)



Patients at risk:

VERZENIO plus fulvestrant										
446	367	314	281	234	171	101	65	32	2	0
Placebo plus fulvestrant										
223	165	123	103	80	61	32	13	4	1	0

Figure 3: Kaplan-Meier Curves of Overall Survival: YULAREB plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)



YULAREB Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. A total of 132 patients received 200 mg YULAREB orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity.

Patient median age was 58 years (range, 36-89 years), and the majority of patients were White (85%). Patients had an Eastern Cooperative Oncology Group performance status of 0 (55% of patients) or 1 (45%). The median duration of metastatic disease was 27.6 months. Ninety percent (90%) of patients had visceral metastases, and 51% of patients had 3 or more sites of metastatic disease. Fifty-one percent (51%) of patients had had one line of chemotherapy in the metastatic setting. Sixty-nine percent (69%) of patients had received a taxane-based regimen in the metastatic setting and 55% had received capecitabine in the metastatic setting. Table 15 provides the efficacy results from MONARCH 1.

Table 15: Efficacy Results in MONARCH 1 (Intent-to-Treat Population)

	YULAREB 200 mg N=132	
	Investigator Assessed	**Independent Review**
Objective Response Rate[a,b], n (%)	26 (19.7)	23 (17.4)
95% CI (%)	13.3, 27.5	11.4, 25.0
Median Duration of Response	8.6 months	7.2 months
95% CI (%)	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached.

[a] All responses were partial responses.

[b] Based upon confirmed responses.

5.2 Pharmacokinetic properties

The pharmacokinetics of abemaciclib were characterized in patients with solid tumors, including metastatic breast cancer, and in healthy subjects.

Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and C_{max} was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on C_{max} and AUC, respectively.

Absorption

The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV). The median T_{max} of abemaciclib is 8.0 hours (range: 4.1-24.0 hours).

Effect of Food

A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC of abemaciclib plus its active metabolites by 9% and increased C_{max} by 26%.

Distribution

In vitro, abemaciclib was bound to human plasma proteins, serum albumin, and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL. In a clinical study, the mean (standard deviation, SD) bound fraction was 96.3% (1.1) for abemaciclib, 93.4% (1.3) for M2, 96.8% (0.8) for M18, and 97.8% (0.6) for M20. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV).

In patients with advanced cancer, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV).

Metabolism

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-

desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). M2, M18, and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively.

Excretion

After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

Specific Populations

Age, Gender, and Body Weight

Based on a population pharmacokinetic analysis in patients with cancer, age (range 24-91 years), gender (134 males and 856 females), and body weight (range 36-175 kg) had no effect on the exposure of abemaciclib.

Patients with Renal Impairment

In a population pharmacokinetic analysis of 990 individuals, in which 381 individuals had mild renal impairment (60 mL/min ≤ CLcr <90 mL/min) and 126 individuals had moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min), mild and moderate renal impairment had no effect on the exposure of abemaciclib *[see Special warnings and precautions for use (4.4)]*. The effect of severe renal impairment (CLcr <30 mL/min) on pharmacokinetics of abemaciclib is unknown.

Patients with Hepatic Impairment

Following a single 200 mg oral dose of abemaciclib, the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, M20) in plasma increased 1.2-fold in subjects with mild hepatic impairment (Child-Pugh A, n=9), 1.1-fold in subjects with moderate hepatic impairment (Child-Pugh B, n=10), and 2.4-fold in subjects with severe hepatic impairment (Child-Pugh C, n=6) relative to subjects with normal hepatic function (n=10) *[see Use in Specific Populations (8.7)]*. In subjects with severe hepatic impairment, the mean plasma elimination half-life of abemaciclib increased to 55 hours compared to 24 hours in subjects with normal hepatic function.

Drug Interaction Studies

Effects of Other Drugs on Abemaciclib

Strong CYP3A Inhibitors: Ketoconazole (a strong CYP3A inhibitor) is predicted to increase the AUC of abemaciclib by up to 16-fold.

Coadministration of 500 mg twice daily doses of clarithromycin (a strong CYP3A inhibitor) with a single 50 mg dose of YULAREB (0.3 times the approved recommended 150 mg dosage) increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 2.5-fold relative to abemaciclib alone in cancer patients.

Moderate CYP3A Inhibitors: Verapamil and diltiazem (moderate CYP3A inhibitors) are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by approximately 1.6-fold and 2.4-fold, respectively.

Strong CYP3A Inducers: Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of YULAREB decreased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by approximately 70% in healthy subjects.

Moderate CYP3A Inducers: Efavirenz, bosentan, and modafinil (moderate CYP3A inducers) are predicted to decrease the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 53%, 41%, and 29%, respectively.

Loperamide: Co-administration of a single 8-mg dose of loperamide with a single 400 mg dose of abemaciclib in healthy subjects increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2 and M20) by 12%, which is not considered clinically relevant.

Endocrine Therapies: In clinical studies in patients with breast cancer, there was no clinically relevant effect of fulvestrant, anastrozole, letrozole, or exemestane on abemaciclib pharmacokinetics.

Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib (2.7 times the approved recommended 150 mg dosage) increased loperamide $AUC_{0\text{-}INF}$ by 9% and C_{max} by 35% relative to loperamide alone. These increases in loperamide exposure are not considered clinically relevant.

Metformin: In a clinical drug interaction study in healthy subjects, coadministration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal OCT2, MATE1, and MATE2-K transporters, with a single 400 mg dose of abemaciclib (2.7 times the approved recommended 150 mg dosage) increased metformin $AUC_{0\text{-}INF}$ by 37% and C_{max} by 22% relative to metformin alone. Abemaciclib reduced the renal clearance and renal secretion of metformin by 45% and 62%, respectively, relative to metformin alone, without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C.

Endocrine Therapies: In clinical studies in patients with breast cancer, there was no clinically relevant effect of abemaciclib on the pharmacokinetics of fulvestrant, anastrozole, letrozole, or exemestane.

CYP Metabolic Pathways: In a clinical drug interaction study in patients with cancer, multiple doses of abemaciclib (200 mg twice daily for 7 days) did not result in clinically meaningful changes in the pharmacokinetics of CYP1A2, CYP2C9, CYP2D6 and CYP3A4 substrates. Abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism were not observed.

In Vitro Studies

Transporter Systems: Abemaciclib and its major active metabolites inhibit the renal transporters OCT2, MATE1, and MATE2-K at concentrations achievable at the approved recommended dosage. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K *[see Special warnings and precautions for use (4.4)]*. Abemaciclib and its major metabolites at clinically relevant concentrations do not inhibit the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 or the renal uptake transporters OAT1 and OAT3.

Abemaciclib is a substrate of P-gp and BCRP. Abemaciclib and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

Abemaciclib inhibits P-gp and BCRP. The clinical consequences of this finding on sensitive P-gp and BCRP substrates are unknown.
P-gp and BCRP Inhibitors: In vitro, abemaciclib is a substrate of P-gp and BCRP. The effect of P-gp or BCRP inhibitors on the pharmacokinetics of abemaciclib has not been studied.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with abemaciclib.

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 was not clastogenic in an in vivo rat bone marrow micronucleus assay.

Studies to assess the effects of abemaciclib on fertility have not been performed. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

YULAREB (abemaciclib) tablets are provided as immediate-release oval white, beige, or yellow tablets. Inactive ingredients are as follows: Excipients—microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide. Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow (50 , 150, 200 mg), and iron oxide red (50, 150 mg).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Aluminium/aluminium perforated unit dose blisters of 7 x 1 film-coated tablets, in packs of 14 or 28 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Zuellig Pharma LTD

No. 2 Ploenchit center, 8th-9th fl, Sukhumvit Rd.,

Klong Toey, Khet Klong Toey

Bangkok Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C XXXXXX (NC) for YULAREB 50 mg
1C XXXXXX (NC) for YULAREB 100 mg
1C XXXXXX (NC) for YULAREB 150 mg
1C XXXXXX (NC) for YULAREB 200 mg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

12 September 2020