NAME OF THE MEDICINAL PRODUCT

YULAREB FILM-COATED TABLET 50MG
YULAREB FILM-COATED TABLET 100MG
YULAREB FILM-COATED TABLET 150MG

QUALITATIVE AND QUANTITATIVE COMPOSITION

YULAREB FILM-COATED TABLET 50MG
Each film-coated tablet contains 50 mg abemaciclib.

YULAREB FILM-COATED TABLET 100MG
Each film-coated tablet contains 100 mg abemaciclib.

YULAREB FILM-COATED TABLET 150MG
Each film-coated tablet contains 150 mg abemaciclib.

1 INDICATIONS AND USAGE

1.1 Early Breast Cancer

Yulareb (abemaciclib) 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 14.1).

1.2 Advanced or Metastatic Breast Cancer

Yulareb (abemaciclib) is indicated:

- 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

- When used in combination with fulvestrant, tamoxifen or an aromatase inhibitor, the recommended dose of Yulareb is 150mg taken orally twice daily. Refer to the Full Prescribing Information for the recommended dose of fulvestrant, or tamoxifen or aromatase inhibitor being used.
- Pre/perimenopausal women treated with the combination of Yulareb plus endocrine therapy should be treated with a gonadotropin-releasing hormone agonist according to current clinical practice standards.
- For early breast cancer, Yulareb should be taken continuously for two years or until disease recurrence, or unacceptable toxicity.
- For advanced or metastatic breast cancer, continue treatment until disease progression or unacceptable toxicity.

Yulareb may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

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.

2.2 Dose Modification

Dose Modifications for Adverse Reactions

The recommended Yulareb dose modifications for adverse reactions are provided in Tables 1-7. Discontinue Yulareb for patients unable to tolerate 50mg twice daily.

Table 1: Yulareb Dose Modification – Adverse Reactions

Dose Level	**Yulareb Dose** **Combination with Fulvestrant, Tamoxifen, or an Aromatase Inhibitor**
Recommended starting dose	150mg twice daily
First dose reduction	100mg twice daily
Second dose reduction	50mg twice daily
Third dose reduction	not applicable

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 – Interstitial Lung Disease (ILD)/ 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 (1, 2, 3 or 4)	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 – 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, ILD / pneumonitis, and VTEs.

Refer to the Full Prescribing Information for coadministered fulvestrant, tamoxifen or 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 150mg twice daily, reduce the Yulareb dose to 100mg twice daily. In patients who have had a dose reduction to 100mg twice daily due to adverse reactions, further reduce the Yulareb dose to 50mg twice daily. 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 strong inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

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 Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

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

3 DOSAGE FORMS AND STRENGTHS

50mg film-coated tablets: Modified oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

100mg film-coated tablets: Modified oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

150mg film-coated tablets: Modified oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *Section 11, Description*.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Severe diarrhea associated with dehydration and infection occurred in patients treated with Yulareb.

Across four clinical trials in 3691 patients, diarrhea occurred in 81% to 90% of patients who received Yulareb. Grade 3 diarrhea occurred in 8% to 20% of patients receiving Yulareb *[see Adverse Reactions (6.1)]*.

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

Instruct patients to start antidiarrheal therapy such as loperamide at the first sign of loose stools, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow up *[see Patient Counseling Information (17)].* 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 Dosage and Administration (2.2)]*.

5.2 Neutropenia

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

Across four clinical trials in 3691 patients, neutropenia occurred in 37% to 46% of patients receiving Yulareb. A Grade ≥ 3 decrease in neutrophil count (based on laboratory findings) occurred in 19% to 32% of patients receiving Yulareb. Across trials, 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 *[see Adverse Reactions (6.1)]*. Higher incidences of Grade ≥ 3 neutropenia and leukopenia were observed in the Asian population as compared with the White population. These did not translate into meaningful differences in the incidences of Grade ≥ 3 infections, SAEs of infection, or discontinuations due to infection.

Febrile neutropenia has been reported in < 1% of patients exposed to Yulareb across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider *[see Patient Counseling Information (17)]*.

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 Dosage and Administration (2.2)]*.

5.3 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. In Yulareb-treated patients in early breast cancer (monarchE, N=2791), 3% of patients experienced ILD/pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%).

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 Dosage and Administration (2.2)]*.

5.4 Hepatotoxicity

Grade ≥3 ALT (2% to 6%) and AST (2% to 3%) were reported in patients receiving Yulareb.

Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), 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. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or any Grade 3 or Grade 4 hepatic transaminase elevation *[see Dosage and Administration (2.2)]*.

5.5 Venous Thromboembolism

Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), venous thromboembolic events were reported in 2% to 5% of patients treated with YULAREB. 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. In clinical trials, deaths due to venous thromboembolism have been reported in patients treated with Yulareb.

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 Dosage and Administration (2.2)]*.

5.6 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 Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

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

- Diarrhea *[see Warnings and Precautions (5.1)]*.
- Neutropenia *[see Warnings and Precautions (5.2)]*.
- Interstitial Lung Disease (ILD)/ Pneumonitis *[see Warnings and Precautions (5.3)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolism *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Studies Experience

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.

Early Breast Cancer

monarchE: Yulareb in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment

Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence

The safety of Yulareb was evaluated in monarchE, a study of 5591 adult patients receiving Yulareb plus endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine therapy (tamoxifen or an aromatase inhibitor) alone *[see Clinical Studies (14.1)]*. Patients were randomly assigned to receive 150 mg of Yulareb orally, twice daily, plus tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of Yulareb treatment was 24 months.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, leukopenia, and diarrhea, and lymphopenia.

Fatal adverse reactions occurred in 0.8% of patients who received Yulareb plus endocrine therapy (tamoxifen or an aromatase inhibitor), including: cardiac failure (0.1%), cardiac arrest, myocardial infarction, ventricular fibrillation, cerebral hemorrhage, cerebrovascular accident, pneumonitis, hypoxia, diarrhea and mesenteric artery thrombosis (0.03% each).

Permanent Yulareb treatment discontinuation due to an adverse reaction was reported in 19% of patients receiving Yulareb, plus tamoxifen or an aromatase inhibitor. Of the patients receiving tamoxifen or an aromatase inhibitor, 1% permanently discontinued due to an adverse reaction. The most common adverse reactions leading to Yulareb discontinuations were diarrhea (5%), fatigue (2%), and neutropenia (0.9%).

Dose reductions of Yulareb due to an adverse reaction occurred in 44% of patients receiving Yulareb plus endocrine therapy (tamoxifen or an aromatase inhibitor). Adverse reactions leading to Yulareb dose reductions in ≥5% were diarrhea (17%), neutropenia (8%), and fatigue (5%).

The most common adverse reactions reported (≥20%) in the YULAREB, plus tamoxifen or an aromatase inhibitor, arm and ≥2% higher than the tamoxifen or an aromatase inhibitor arm were diarrhea, infections, neutropenia, fatigue, leukopenia, nausea, anemia, and headache. Adverse reactions are shown in Table 8 and laboratory abnormalities are shown in Table 9.

The safety profile for men treated with YULAREB in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) is consistent with that observed in women.

Table 8: Adverse Reactions ≥10% of Patients Receiving Yulareb Plus Endocrine Therapy (Tamoxifen or an Aromatase Inhibitor) [with a Difference between Arms of ≥2%] in monarchE

	Yulareb Plus Endocrine Therapy (Tamoxifen or an Aromatase Inhibitor) N=2791			Endocrine Therapy (Tamoxifen or an Aromatase Inhibitor) N=2800		
	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[b] %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	84	8	0	9	0.2	0
Nausea	30	0.5	0	9	0.1	0
Vomiting	18	0.5	0	4.6	0.1	0
Stomatitis[c]	14	0.1	0	5	0	0
Infections and Infestations						
Infections[d]	51	4.9	0.6	39	2.7	0.1
General Disorders and Administration Site Conditions						
Fatigue[e]	41	2.9	0	18	0.1	0
Nervous System Disorders						
Headache	20	0.3	0	15	0.2	0
Dizziness	11	0.1	0	7	0.1	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	0.6	0	2.4	0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash[f]	11	0.4	0	4.5	0	0
Alopecia	11	0	0	2.7	0	0

[a] Includes the following fatal adverse reactions: diarrhea (n=1), and infections (n=4)

[b] Includes the following fatal adverse reactions: infections (n=5)

[c] Includes mouth ulceration, mucosal inflammation, oropharyngeal pain, stomatitis.

[d] Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>5%) include upper respiratory tract infection, urinary tract infection, and nasopharyngitis.

[e] Includes asthenia, fatigue.

[f] Includes exfoliative rash, mucocutaneous rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash vesicular, vulvovaginal rash.

Clinically relevant adverse reactions in <10% of patients who received YULAREB in combination with tamoxifen or an aromatase inhibitor in monarchE include:

- Pruritus-9%
- Dyspepsia-8%
- Nail disorder-6% (includes nail bed disorder, nail bed inflammation, nail discoloration, nail disorder, nail dystrophy, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis)
- Lacrimation increased-6%
- Dysgeusia-5%
- Interstitial lung disease (ILD)/pneumonitis-3% (includes pneumonitis, radiation pneumonitis, interstitial lung disease, pulmonary fibrosis, organizing pneumonia, radiation fibrosis – lung, lung opacity, sarcoidosis)
- Venous thromboembolic events (VTEs)-3% (includes catheter site thrombosis, cerebral venous thrombosis, deep vein thrombosis, device related thrombosis, embolism, hepatic vein thrombosis, jugular vein occlusion, jugular vein thrombosis, ovarian vein thrombosis, portal vein thrombosis, pulmonary embolism, subclavian vein thrombosis, venous thrombosis limb)

Table 9: Laboratory Abnormalities (≥10%) in Patients Receiving Yulareb Plus Endocrine Therapy Therapy (Tamoxifen or an Aromatase Inhibitor) [with a Difference between Arms of ≥2%] in monarchE

	Yulareb Plus Tamoxifen or Aromatase Inhibitor N=2791			Tamoxifen or Aromatase Inhibitor N=2800		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	99	<1	0	91	<1	0
White blood cell decreased	89	19	<1	28	1	0
Neutrophil count decreased	84	18	<1	23	2	<1
Anemia	68	1	0	17	<1	0
Lymphocyte count decreased	59	13	<1	24	2	<1
Platelet count decreased	37	<1	<1	10	<1	<1
Alanine aminotransferase increased	37	3	<1	24	1	0
Aspartate aminotransferase increased	31	2	<1	18	<1	0
Hypokalemia	11	1	<1	4	<1	<1

Advanced or Metastatic Breast Cancer

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

The safety of Yulareb was evaluated in MONARCH 3, a study of 488 women receiving Yulareb plus an aromatase inhibitor or placebo plus an aromatase inhibitor *[see Clinical Studies (14.2)]*. 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.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia.

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, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.

Permanent treatment discontinuation due to an adverse reaction 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%).

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.

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). Adverse reactions are shown in Table 10 and laboratory abnormalities in Table 11. 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 Dosage and Administration (2.2) and Patient Counseling Information (17)]*. 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 10: Adverse Reactions ≥ 10% of Patients Receiving Yulareb Plus Anastrozole or Letrozole [with a Difference between Arms of ≥2%] 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	1.2	0
Nausea	39	0.9	0	20	1.2	0
Abdominal pain	29	1.2	0	12	1.2	0
Vomiting	28	1.2	0	12	1.9	0
Constipation	16	0.6	0	12	0	0
Infections and Infestations						
Infections[a]	39	4.0	0.9	29	2.5	0.6

	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 %
General Disorders and Administration Site Conditions						
Fatigue	40	1.8	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	0.9	0	5	0	0
Pruritus	13	0	0	9	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	24	1.2	0	9	0.6	0
Investigations						
Weight decreased	10	0.6	0	3.1	0.6	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	9	0	0
Dyspnea	12	0.6	0.3	6	0.6	0
Nervous System Disorders						
Dizziness	11	0.3	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 11: Laboratory Abnormalities ≥ 10% in Patients Receiving Yulareb Plus Anastrozole or Letrozole [with a Difference Between Arms of ≥2%] 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 Clinical Pharmacology (12.3)]*. 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 (150mg twice daily) plus fulvestrant (500mg) versus placebo plus fulvestrant was evaluated in MONARCH 2 *[see Clinical Studies (14.2)]*. 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.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

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.

Permanent study treatment discontinuation due to an adverse reaction 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%).

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.

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. Adverse reactions are shown in Table 12 and laboratory abnormalities in Table 13.

Table 12: Adverse Reactions ≥ 10% in Patients Receiving Yulareb Plus Fulvestrant [with a Difference Between Arms of ≥2%] 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	0.4	0
Nausea	45	2.7	0	23	0.9	0
Abdominal pain[a]	35	2.5	0	16	0.9	0
Vomiting	26	0.9	0	10	1.8	0
Stomatitis	15	0.5	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	0.7	25	3.1	0.4
General Disorders and Administration Site Conditions						
Fatigue[c]	46	2.7	0	32	0.4	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	0.5	0.2	6	0.4	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1.1	0	12	0.4	0

	Yulareb plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	1.8	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1.1	0	4.5	0	0
Nervous System Disorders						
Headache	20	0.7	0	15	0.4	0
Dysgeusia	18	0	0	2.7	0	0
Dizziness	12	0.7	0	6	0	0
Investigations						
Weight decreased	10	0.2	0	2.2	0.4	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 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 13: Laboratory Abnormalities (≥ 10%) in Patients Receiving Yulareb Plus Fulvestrant [with a Difference Between Arms of ≥2%]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 Clinical Pharmacology (12.3)]*. 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.

6.2 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 Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 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 Clinical Pharmacology (12.3)]*.

Other Strong CYP3A Inhibitors

In patients with recommended starting doses of 150mg twice daily, reduce the Yulareb dose to 100mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100mg twice daily due to adverse reactions, further reduce the Yulareb dose to 50mg twice daily with concomitant use of other 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 Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

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 CYP3A inducers and consider alternative agents *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 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 Clinical Pharmacology (12.1)]*. 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* Data). 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.

8.2 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.

8.3 Females and Males of Reproductive Potential

Based on animal studies, Yulareb can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with Yulareb.

Contraception

Females

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 Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 2791 YULAREB-treated patients in monarchE, 15% were 65 years of age or older and 2.7% were 75 years of age or older.

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

8.6 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 Clinical Pharmacology (12.3)]*.

8.7 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 Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

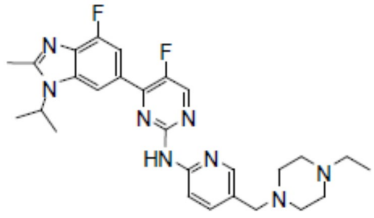
10 OVERDOSAGE

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

11 DESCRIPTION

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:



Yulareb (abemaciclib) film-coated tablets are provided as immediate-release, modified 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 (present in 50mg and 150mg), and iron oxide red (present in 50mg).

12 CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Antineoplastic agents, protein kinases inhibitors, ATC code: L01EF03

12.1 Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), and most active against Cyclin D1/CDK4 in enzymatic assays. 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.

12.2 Pharmacodynamics

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.

12.3 Pharmacokinetics

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

Following single and repeated twice daily dosing of 50mg (0.3 times the approved recommended 150mg dosage), 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 200mg 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 150mg 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 Use in Specific Populations (8.6)]*. The effect of severe renal impairment (CLcr < 30 mL/min) on pharmacokinetics of abemaciclib is unknown.

Patients with Hepatic Impairment

Following a single 200mg 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 500mg twice daily doses of clarithromycin (a strong CYP3A inhibitor) with a single 50mg dose of Yulareb (0.3 times the approved recommended 150mg 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 600mg daily doses of rifampin (a strong CYP3A inducer) with a single 200mg 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 400mg 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, exemestane, or tamoxifen on abemaciclib pharmacokinetics.

Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, coadministration of a single 8mg dose of loperamide with a single 400mg abemaciclib (2.7 times the approved recommended 150mg 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 1000mg dose of metformin, a clinically relevant substrate of renal OCT2, MATE1, and MATE2-K transporters, with a single 400mg dose of abemaciclib (2.7 times the approved recommended 150mg 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, exemestane, or tamoxifen.

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 Adverse Effects (6.1)]. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Abemaciclib was assessed for carcinogenicity in 2-year studies in rats and mice. In male rats, daily oral administration of abemaciclib resulted in benign testicular interstitial cell adenomas at exposures approximately 1.5 times human clinical exposure. In addition, interstitial cell hyperplasia was observed at exposures approximately 0.1 times human clinical exposure. It is unknown if these effects will translate to humans. There were no neoplastic findings in mice or in female rats that were due to administration of 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.

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).

13.2 Animal Toxicology and/or Pharmacology

In repeat-dose toxicity studies up to 6-months duration, oral administration of abemaciclib resulted in retinal atrophy of the eyes in mice at a dose of 150 mg/kg/day (approximately 10 times the exposure at the maximum recommended human dose based on AUC) and in rats at a dose of 30 mg/kg/day (approximately 5 times the exposure at the maximum recommended human dose based on AUC). In a 2-year rat carcinogenicity study, oral administration of abemaciclib resulted in retinal atrophy in the eyes at doses ≥0.3 mg/kg/day (approximately 0.05 times the exposure at the maximum recommended human dose based on AUC).

In a 6-month repeat-dose study in rats, administration of abemaciclib caused minimal inflammation, observed concurrently with vacuolated macrophages, within heart valves in male rats treated at 30 mg/kg/day (approximately 8-fold higher than human exposure at 150 mg BID).

14 CLINICAL STUDIES

14.1 Early Breast Cancer

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

The efficacy and safety of Yulareb 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 Yulareb 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.

The primary objective of the study was met at the pre planned interim analysis (16 Mar 2020 cut-off) . A statistically significant improvement in IDFS was observed in patients who received Yulareb plus endocrine therapy versus endocrine therapy alone in the ITT population.

In a further analysis (01 April 2021 cut-off), 91 % of the patients in Cohort 1 were off the 2- year study treatment period and the median duration of follow-up was 27.7 months.

Efficacy results in Cohort 1 are summarised in Table 16 and Figure 1.

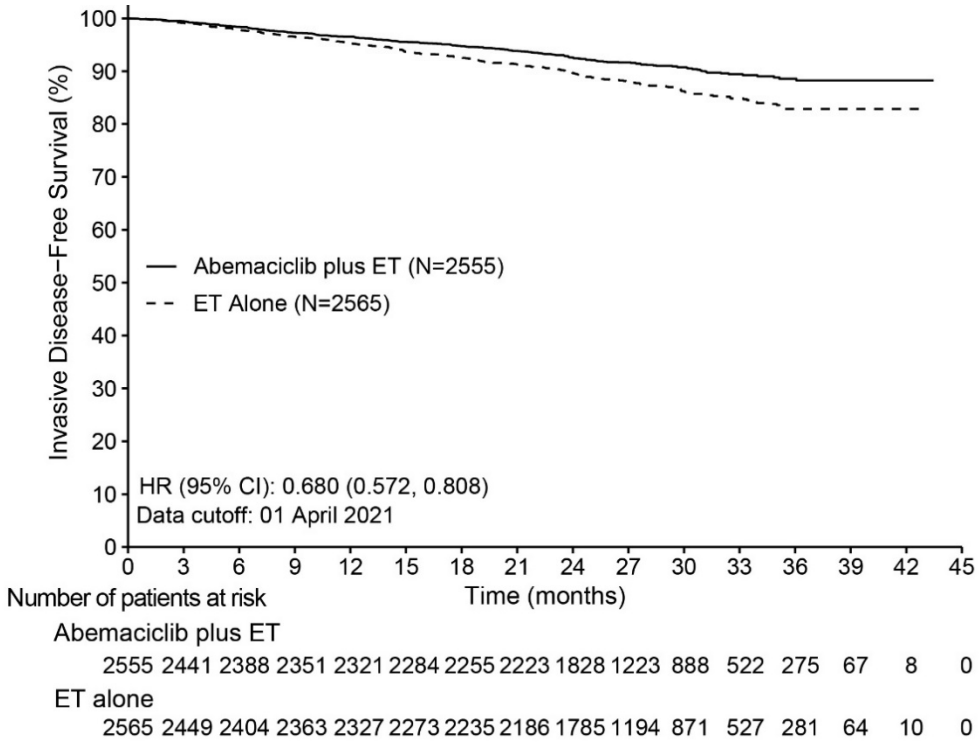
Table 16. monarchE: Summary of efficacy data (Cohort 1 population)

	Yulareb 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.

Data cut-off date 01 Apr 2021

Figure 1. monarchE: Kaplan-Meier plot of IDFS (Investigator assessment, Cohort 1 population)



Abbreviations: CI = confidence interval; ET = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; N = number of patients in the population.

Data cut-off date 01 April 2021

Benefit was observed across patient subgroups defined by geographic region, menopausal status and prior chemotherapy within Cohort 1.

14.2 Advanced or Metastatic Breast Cancer

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 (NCT02246621) 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 150mg 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 17 and Figure 2. 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 17: Efficacy Results in MONARCH 3 (Investigator Assessment, Intent-to-Treat Population)

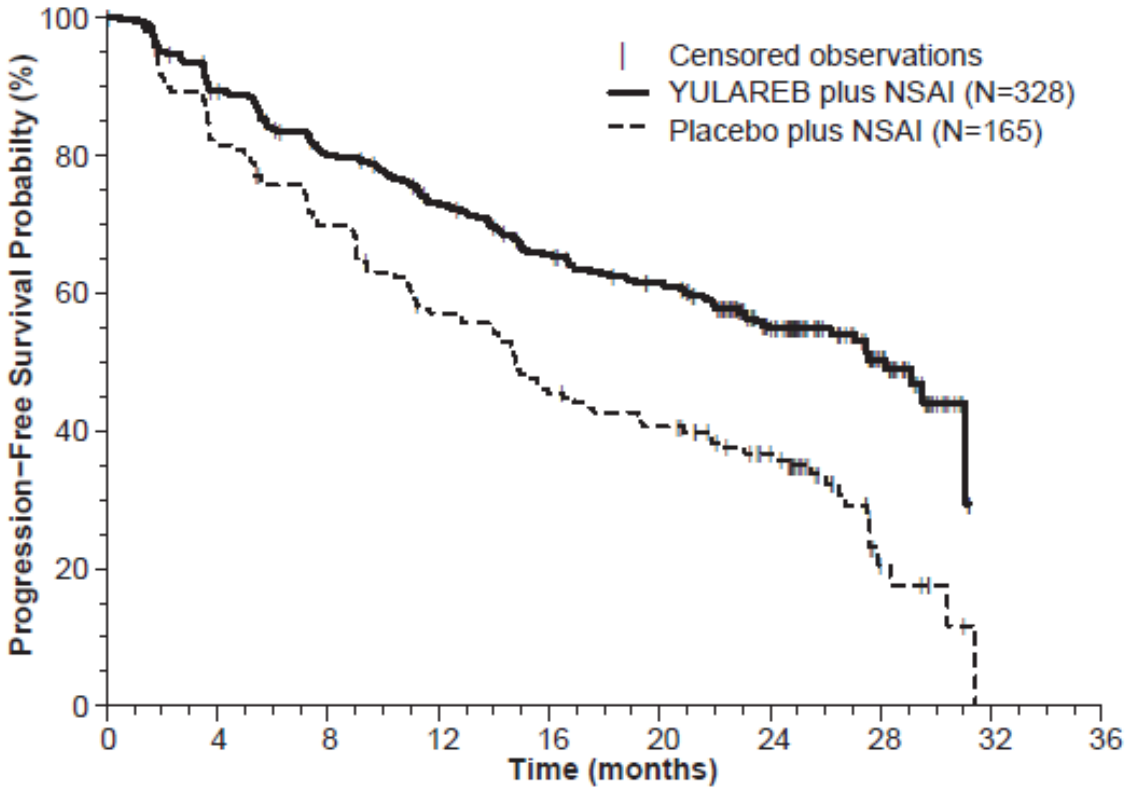
	Yulareb plus Anastrozole or Letrozole	**Placebo plus Anastrozole or Letrozole**
Progression-Free Survival	**N=328**	**N=165**
Number of patients with an event (n, %)	138 (42.1)	108 (65.5)
Median (months, 95% CI)	28.2 (23.5, NR)	14.8 (11.2, 19.2)
Hazard ratio (95% CI)	0.540 (0.418, 0.698)	
p-value	< 0.0001	
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 2: 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 500mg 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 18, Figure 3 and Figure 4. 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 18: 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 therapyresistance (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 3: Kaplan-Meier Curves of Progression-Free Survival: Yulareb plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)

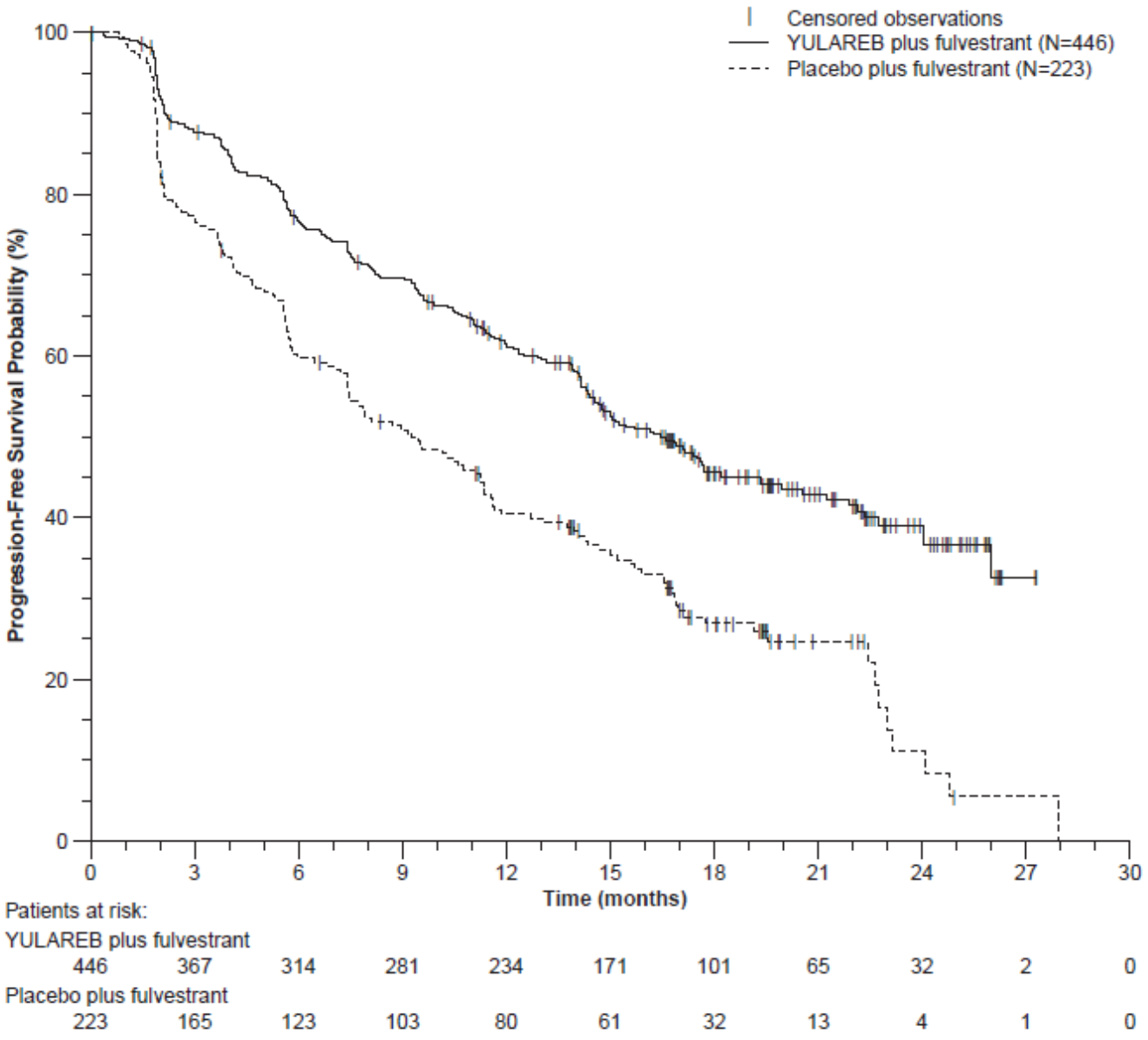
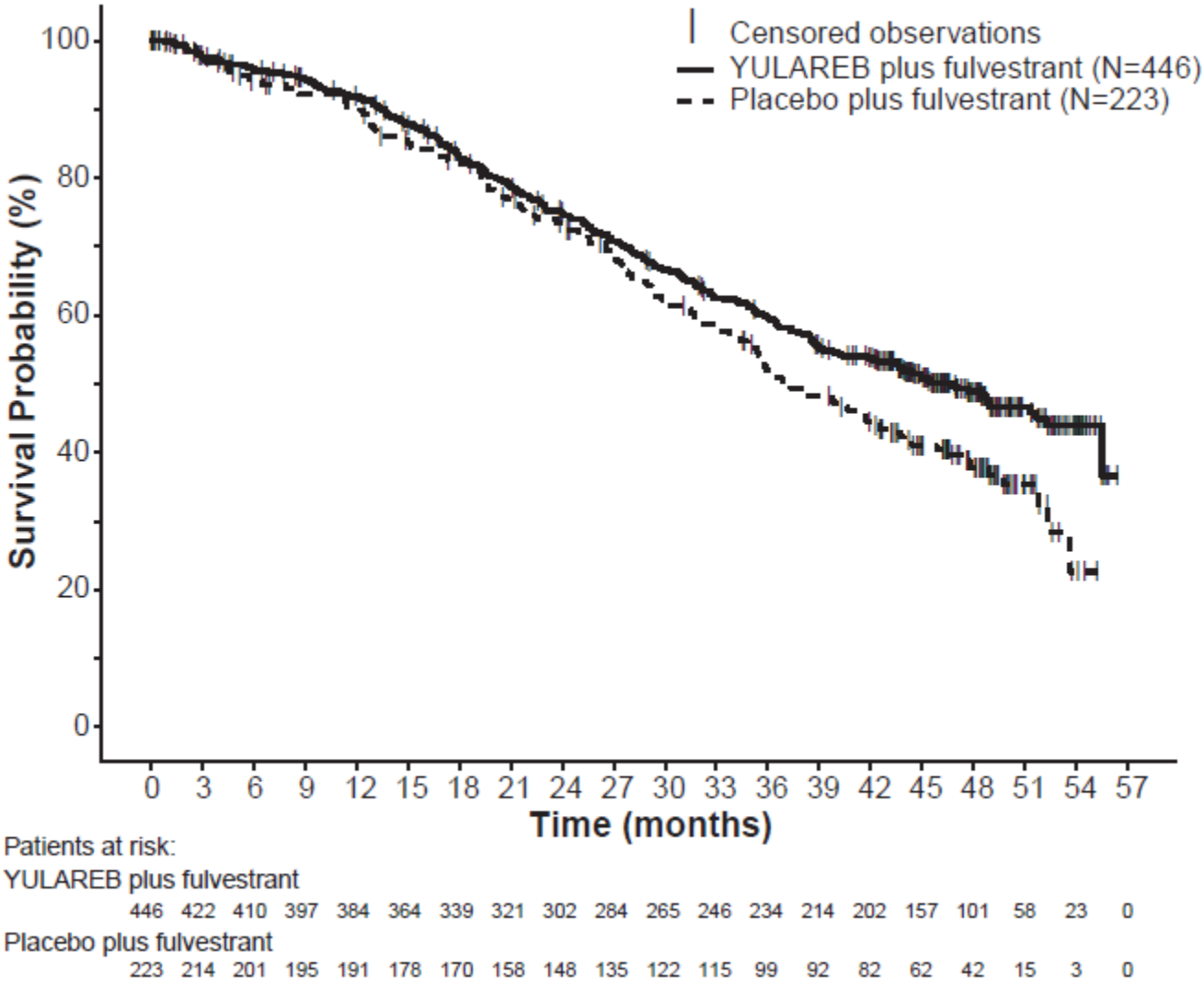


Figure 4: Kaplan-Meier Curves of Overall Survival: YULAREB plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Yulareb tablets are supplied in blister strip cold form aluminium foil (CFAF) sealed with aluminium foil lidding, in carton of 14 film-coated tablets.

16.2 Storage and Handling

Store below 30° C.

17 PATIENT COUNSELING INFORMATION

Diarrhea

Yulareb may cause diarrhea, which may be severe in some cases *[see Warnings and Precautions (5.1)]*.

- Early identification and intervention is critical for the optimal management of diarrhea. Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy (for example, loperamide) and notify their healthcare provider for further instructions and appropriate follow up.
- Encourage patients to increase oral fluids.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to ≤Grade 1, suspend Yulareb dosing *[see Dosage and Administration (2.2)]*.

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 *[see Warnings and Precautions (5.2)]*.

Interstitial Lung Disease/Pneumonitis

Advise patients to immediately report new or worsening respiratory symptoms *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.4)]*.

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 *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)]*.

- Advise females of reproductive potential to use effective contraception during Yulareb treatment and for 3 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise lactating women not to breastfeed during Yulareb treatment and for at least 3 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Inform males of reproductive potential that Yulareb may impair fertility *[see Use in Specific Populations (8.3)]*.

Drug Interactions

- Inform patients to avoid concomitant use of ketoconazole. Dose reduction may be required for other strong CYP3A inhibitors or for moderate CYP3A inhibitors *[see Dosage and Administration (2.2) and Drug Interactions (7)]*.
- Grapefruit may interact with Yulareb. Advise patients not to consume grapefruit products while on treatment with Yulareb.
- Advise patients to avoid concomitant use of strong and moderate CYP3A inducers and to consider alternative agents *[see Dosage and Administration (2.2) and Drug Interactions (7)]*.
- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Dosage and Administration (2.2) and Drug Interactions (7)]*.

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) *[see Dosage and Administration (2.1)]*.
- If patient vomits or misses a dose, advise the patient to take the next prescribed dose at the usual time *[see Dosage and Administration (2.1)]*.
- Advise the patient that Yulareb may be taken with or without food *[see Dosage and Administration (2.1)]*.

18 PRODUCT OWNER

Eli Lilly and Company, Indianapolis, IN 46285, USA

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