YULAREB
Abemaciclib 50

1. NAME OF THE MEDICINAL PRODUCT

Yulareb 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yulareb 50 mg film-coated tablets

Each film-coated tablet contains 50 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 14 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yulareb 50 mg film-coated tablets

Beige, oval tablet of 5.2 x 9.5 mm, debossed with “Lilly” on one side and “50” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Early Breast Cancer
Yulareb in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) is indicated for the adjuvant treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−), node-positive early breast cancer at high risk of recurrence.

High risk of recurrence 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; or 1-3 pALN and high Ki-67 index (≥20%) [see Dosage and Administration and Clinical Studies]

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

Advanced or Metastatic Breast Cancer
Yulareb is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer:
- in combination with an aromatase inhibitor as initial endocrine-based therapy
- in combination with fulvestrant as initial endocrine-based therapy or in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

Note: for women <60 years old, serum FSH and estradiol should be measured to assure postmenopausal status, unless bilateral oophorectomy has been done.

4.2 Posology and method of administration

Yulareb therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

Posology

Yulareb in combination with endocrine therapy
The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Please refer to the Summary of Product Characteristics of the endocrine therapy combination partner for the recommended posology.

Duration of treatment

Early Breast Cancer
Yulareb should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs.

Advanced or Metastatic Breast Cancer
Yulareb should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

If a patient vomits or misses a dose of Yulareb, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Dose adjustments
Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1-7.

Table 1: Dose adjustment recommendations for adverse reactions

	Yulareb dose combination therapy
Recommended dose	150 mg twice daily
First dose adjustment	100 mg twice daily
Second dose adjustment	50 mg twice daily

Table 2: Management recommendations for haematologic toxicities
Complete blood counts should be monitored prior to the start of Yulareb therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated. Before treatment initiation, absolute neutrophil counts (ANC) ≥1 500/mm^3, platelets ≥1 00 000/mm^3, and haemoglobin ≥ 8 g/dL are recommended.

Toxicity[a, b]	**Management recommendations**
Grade 1 or 2	No dose adjustment required.
Grade 3	Suspend dose until toxicity resolves to Grade 2 or less. Dose reduction is not required.
Grade 3, recurrent; or Grade 4	Suspend dose until toxicity resolves to Grade 2 or less. Resume at next lower dose.
Patient requires administration of blood cell growth factors	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade 2 or less. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

[a] NCI Common Terminology Criteria for Adverse Events (CTCAE)
[b] ANC: Grade 1: ANC < LLN – 1 500 / mm^3; Grade 2: ANC 1 000 - < 1 500 / mm^3; Grade 3: ANC 500 - < 1 000 / mm3; Grade 4: ANC < 500 / mm^3
LLN = lower limit of normal

Table 3: Management recommendations for diarrhoea

Treatment with antidiarrhoeal agents, such as loperamide, should be started at the first sign of loose stools.

Toxicity[a]	**Management recommendations**
Grade 1	No dose adjustment required.
Grade 2	If toxicity does not resolve within 24 hours to Grade 1 or less, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4 or requires hospitalisation	

[a] NCI CTCAE

Table 4: Management recommendations for increased aminotransferases

Alanine aminotransferase (ALT) and aspartate aminostransferase (AST) should be monitored prior to the start of Yulareb therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

Toxicity[a]	Management recommendations
Grade 1 (>ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	No dose adjustment required.
Persistent or Recurrent Grade 2, or Grade 3 (> 5.0 - 20.0 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 abemaciclib.
Grade 4 (> 20.0 x ULN)	Discontinue abemaciclib.

[a] NCI CTCAE
ULN = upper limit of normal

Table 5. Management recommendations for interstitial lung disease (ILD)/pneumonitis

Toxicity[a]	Management recommendations
Grade 1 or 2	No dose adjustment 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 abemaciclib.

[a] NCI CTCAE

Table 6. Management recommendations for venous thromboembolic events (VTEs)

Toxicity[a]	Management recommendations
Early Breast Cancer	
All Grades (1, 2, 3, or 4)	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed 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. Abemaciclib may be resumed when the patient is clinically stable.

[a] NCI CTCAE

Table 7: Management recommendations for non-haematologic toxicities (excluding diarrhea, increased aminotransferases, and ILD/pneumonitis and VTEs)

Toxicity[a]	Management recommendations
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4	

[a] NCI CTCAE

CYP3A4 inhibitors
Concomitant use of strong CYP3A4 inhibitors should be avoided. If strong CYP3A4 inhibitors cannot be avoided, the abemaciclib dose should be reduced to 100 mg twice daily.

In patients who have had their dose reduced to 100 mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose should be further reduced to 50 mg twice daily.

In patients who have had their dose reduced to 50 mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose may be continued with close monitoring of signs of toxicity. Alternatively, the abemaciclib dose may be reduced to 50 mg once daily or discontinued.

If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor).

Special populations

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

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

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

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

No data are available.

Method of administration

Yulareb is for oral use.

The dose can be taken with or without food. It should not be taken with grapefruit or grapefruit juice (see section 4.5).

Patients should take the doses at approximately the same times every day.

The tablet should be swallowed whole (patients should not chew, crush, or split tablets before swallowing).

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

Neutropenia

Neutropenia was reported in patients receiving abemaciclib. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2). Fatal events of neutropenic sepsis occurred in < 1% of patients with metastatic breast cancer. Patients should be instructed to report any episode of fever to their healthcare provider.

Infections/infestations

Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in < 1% of patients with metastatic breast cancer. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with abemaciclib plus endocrine therapy. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate. Based on the grade of VTE, abemaciclib may require dose modification (see section 4.2).

Increased aminotransferases

Increases in ALT and AST were reported in patients receiving abemaciclib. Based on the level of ALT or AST elevation, abemaciclib may require dose modification (see section 4.2).

Diarrhoea

Diarrhoea is the most common adverse reaction. Across clinical studies, median time to onset of the first diarrhoea event was approximately 6 to 8 days, and median duration of diarrhoea was 7 to 12 days (Grade 2) and 5 to 8 days (Grade 3). Diarrhoea can be associated with dehydration. Patients should start treatment with antidiarrhoeal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop ≥ Grade 2 diarrhoea (see section 4.2).

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis was reported in patients receiving abemaciclib. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and treat as medically appropriate. Based on the grade of ILD/pneumonitis,

abemaciclib may require dose modification (see section 4.2). Permanently discontinue abemaciclib in patients with Grade 3 or 4 ILD/pneumonitis.

Concomitant use of inducers of CYP3A4

Concomitant use of CYP3A4 inducers should be avoided due to the risk of decreased efficacy of abemaciclib (see section 4.5).

Visceral crisis

There are no data on the efficacy and safety of abemaciclib in patients with visceral crisis.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on the pharmacokinetics of abemaciclib

Abemaciclib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors
Co-administration of abemaciclib with CYP3A4 inhibitors can increase plasma concentrations of abemaciclib. In patients with advanced and/or metastatic cancer, co-administration of the CYP3A4 inhibitor clarithromycin resulted in a 3.4-fold increase in the plasma exposure of abemaciclib and a 2.5-fold increase in the combined unbound potency adjusted plasma exposure of abemaciclib and its active metabolites.

Use of strong CYP3A4 inhibitors together with abemaciclib should be avoided. If strong CYP3A4 inhibitors need to be co-administered, the dose of abemaciclib should be reduced (see section 4.2), followed by careful monitoring of toxicity. Examples of strong CYP3A4 inhibitors include, but not limited to: clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole or voriconazole. Avoid grapefruit or grapefruit juice.

No dose adjustment is necessary for patients treated with moderate or weak CYP3A4 inhibitors. There should, however, be close monitoring for signs of toxicity.

CYP3A4 inducers
Co-administration of abemaciclib with the strong CYP3A4 inducer rifampicin decreased the plasma concentration of abemaciclib by 95 % and unbound potency adjusted plasma concentration of abemaciclib plus its active metabolites by 77 % based on $AUC_{0-\infty}$. Concomitant use of strong CYP3A4 inducers (including, but not limited to: carbamazepine, phenytoin, rifampicin and St. John's wort) should be avoided due to the risk of decreased efficacy of abemaciclib.

Effects of abemaciclib on the pharmacokinetics of other medicinal products

Medicinal products that are substrates of transporters
Abemaciclib and its major active metabolites inhibit the renal transporters organic cation transporter 2 (OCT2), multidrug and extrusion toxin protein (MATE1), and MATE2-K. *In vivo* interactions of abemaciclib with clinically relevant substrates of these transporters, such as dofetilide or creatinine, may occur (see section 4.8). In a clinical drug interaction study with metformin (substrate of OCT2, MATE1 and 2) co-administered with 400 mg abemaciclib, a small but not clinically relevant increase (37 %) in metformin plasma exposure was observed. This was found to be due to reduced renal secretion with unaffected glomerular filtration.

In healthy subjects, co-administration of abemaciclib and the P-glycoprotein (P-gp) substrate loperamide resulted in an increase in loperamide plasma exposure of 9% based on $AUC_{0-\infty}$ and 35 % based on C_{max}. This was not considered to be clinically relevant. However, based on the *in vitro* inhibition of P-gp and breast cancer resistance protein (BCRP) observed with abemaciclib, *in vivo* interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin or dabigatran etexilate, may occur.

In a clinical study in patients with breast cancer, there was no clinically-relevant pharmacokinetic drug interaction between abemaciclib and anastrozole, fulvestrant, exemestane, letrozole or tamoxifen.

It is currently unknown whether abemaciclib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives are advised to add a barrier method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should use highly effective contraception methods (e.g. double-barrier contraception) during treatment and for at least 3 weeks after completing therapy (see section 4.5).

Pregnancy

There are no data from the use of abemaciclib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Yulareb is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

It is unknown whether abemaciclib is excreted in human milk. A risk to newborns/infants cannot be excluded. Patients receiving abemaciclib should not breast-feed.

Fertility

The effect of abemaciclib on fertility in humans is unknown. In animal studies, no effects on female reproductive organs were observed. However, cytotoxic effects to the male reproductive tract in rats and dogs indicate that abemaciclib may impair fertility in males (see section 5.3).

4.7 Effects on ability to drive and use machines

Yulareb has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with Yulareb (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated list of adverse reactions

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

Table 8. Adverse reactions reported in the phase 3 studies of abemaciclib in combination with endocrine therapy[a] (N = 3559)

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

Investigations	Alanine aminotransferase increased [g] Aspartate aminotransferase increased [g]		

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

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

[c] Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis.

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

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

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

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

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

Description of selected adverse reactions

Neutropenia
Neutropenia was reported frequently across studies. In the monarchE study, neutropenia was reported in 45.8 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 19.1 % of patients receiving abemaciclib in combination with endocrine therapy with a median time to onset of 30 days, and median time to resolution of 16 days. Febrile neutropenia was reported in 0.3 % patients. In MONARCH2 and MONARCH3 studies, neutropenia was reported in 45.1% of patients Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28.2% of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile neutropenia was reported in 0.9 % patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2).

Diarrhoea
Diarrhoea was the most commonly reported adverse reaction (see Table 8). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. In the monarchE study, the median time to onset of the first diarrhoea event of any grade was 8 days. The median duration of diarrhoea was 7 days for Grade 2 and 5 days for Grade 3. In MONARCH2 and MONARCH3 studies, the median time to onset of the first diarrhoea event of any grade was approximately 6 to 8 days. The median duration of diarrhoea was 9 to 12 days for Grade 2 and 6 to 8 days for Grade 3. Diarrhoea returned to baseline or lesser grade with supportive treatment such as loperamide and/or dose adjustment (see section 4.2).

Increased aminotransferases
In the monarchE study, ALT and AST elevations were reported frequently (12.3 % and 11.8 %, respectively) in patients receiving abemaciclib in combination with endocrine therapy. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 2.6 % and 1.6 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 118 days, and median time to resolution was 14.5 days. The median time to onset of Grade 3 or 4 AST elevation was 90.5 days, and median time to resolution was 11 days. In MONARCH2 and MONARCH3 studies, ALT and AST elevations were reported

frequently (15.1 % and 14.2 %, respectively) in patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6.1 % and 4.2 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2).

Creatinine
Although not an adverse reaction, abemaciclib has been shown to increase serum creatinine. In the monarchE study, 99.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 0.5 % of patients had Grade 3 or 4 elevations. In patients receiving endocrine therapy alone, 91.0 % reported an increase in serum creatinine (all laboratory grades). In MONARCH 2 and MONARCH3 studies, 98.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 1.9 % of patients had Grade 3 or 4 elevations . In patients receiving an aromatase inhibitor or fulvestrant alone, 78.4 % reported an increase in serum creatinine (all laboratory grades). Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance) (see section 4.5). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the following:
Telephone: +62 21 21684084
or
Email: IDsafety@zuelligpharma.com

4.9 Overdose

In the event of an abemaciclib overdose, fatigue and diarrhoea may occur. General supportive care should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Abemaciclib is a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), and most active against Cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking cell cycle progression from the G1 to the S-phase of cell division, leading to suppression of tumour growth. In oestrogen receptor-positive breast cancer cell lines, sustained target inhibition with abemaciclib prevented rebound of Rb phosphorylation resulting in cell senescence and apoptosis. *In vitro*, Rb-negative and Rb-depleted cancer cell lines are generally less sensitive to abemaciclib. In breast cancer xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations alone or in combination with anti-oestrogens resulted in reduction of tumour size.

Pharmacodynamic effects

In cancer patients, abemaciclib inhibits CDK4 and CDK6 as indicated by inhibition of phosphorylation of Rb and topoisomerase II alpha, which results in cell cycle inhibition upstream of the G1 restriction point.

Cardiac electrophysiology

The effect of abemaciclib on the QTcF interval was evaluated in 144 patients with advanced cancer. No large change (that is, >20 ms) in the QTcF interval was detected at the mean observed maximal steady state abemaciclib concentration following a therapeutic dosing schedule.
In an exposure-response analysis in healthy subjects at exposures comparable to a 200 mg twice-daily dose, abemaciclib did not prolong the QTcF interval to any clinically relevant extent.

Clinical efficacy and safety

Early Breast Cancer

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

The efficacy and safety of Yularebs in combination with adjuvant endocrine therapy was evaluated in monarchE, a randomised, open label, 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 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; or 1-3 pALN and high Ki-67 index (≥ 20 %).

A total of 5637 patients were randomised in a 1:1 ratio to receive 2 years of Yularebs 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. In both treatment arms patients continued to receive adjuvant endocrine therapy for up to 5-10 years. LHRH agonists were given when clinically indicated to pre- and perimenopausal women, and men.

The randomized population included 5120 (91 %) patients enrolled to the study based on high risk clinical and pathological features, and 517 (9 %) patients enrolled to the study based on 1-3 pALN and high Ki-67 index only.

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 four percent of patients were pre- or perimenopausal. Most patients received prior chemotherapy (37 % neoadjuvant, 62 % adjuvant), and prior radiotherapy (95 %). Initial endocrine therapy received by patients included letrozole (38 %), tamoxifen (31 %), anastrozole (22 %), or exemestane (8 %).
Sixty percent of the patients had 4 or more positive lymph nodes, 38 % had Grade 3 tumour, 22 % had pathological tumour size ≥ 5 cm at surgery, and 44 % had high Ki-67 index in ITT population.

The primary endpoint was invasive disease-free survival (IDFS) 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) 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) with a median follow-up time of 15.5 months. A statistically significant improvement in IDFS was observed in patients who received Yularebs plus endocrine therapy versus endocrine therapy alone (HR = 0.747, 95 % CI [0.598, 0.932], p = 0.0096). These results correspond to clinically meaningful improvement in the 2-year IDFS rate (92.2 % vs 88.7 %) for patients treated with Yularebs plus endocrine therapy. In addition, a clinically meaningful benefit in DRFS (HR = 0.717, 95 % CI [0.559, 0.920]) was observed with Yularebs plus endocrine therapy, reflecting a 28.3 % reduction in the risk of distant recurrence or death. Consistent results were observed in patient subgroups including geographic region, prior chemotherapy, and menopausal status.

Efficacy results for the final IDFS analysis (08 July 2020 cut-off) with a median follow-up of 19.1 months are summarised in Table 9a.

Table 9a. monarchE: Summary of efficacy data at final IDFS analysis (Intent-to-Treat Population)

	Yulareb plus endocrine therapy N = 2808	**Endocrine therapy alone N = 2829**
Invasive disease-free survival (IDFS)		
Number of patients with event (n, %)	163 (5.8)	232 (8.2)
Hazard ratio (95 % CI) and p-value	0.713 (0.583, 0.871), p = 0.00089	
IDFS at 24 months (%, 95 % CI)	92.3 (90.9, 93.5)	89.3 (87.7, 90.7)
Distant relapse free survival (DRFS)		
Number of patients with an event (n, %)	131 (4.7)	193 (6.8)
Hazard ratio (95 % CI)	0.687 (0.551, 0.858)	
DRFS at 24 months (%, 95 % CI)	93.8 (92.6, 94.9)	90.8 (89.3, 92.1)

Abbreviation: CI = confidence interval.

A statistically significant improvement in the final IDFS analysis was also observed in patients in the ITT population with high Ki-67 index (HR of 0.691 [95 % CI: 0.519, 0.920], p = 0.0111).

In a subsequent analysis (01 April 2021 cut-off), 90 % of the patients were off the 2-year study treatment period and the median duration of follow-up was approximately 27 months. The clinical benefit of Yulareb plus endocrine therapy deepened further: the hazard of developing an IDFS event was reduced by 30.4 % (HR = 0.696, 95 % CI [0.588, 0.823]), compared to endocrine therapy alone (Figure 1). In addition, the clinically meaningful benefit in DRFS (HR = 0.687, 95 % CI [0.571, 0.826]) was maintained with Yulareb plus endocrine therapy.

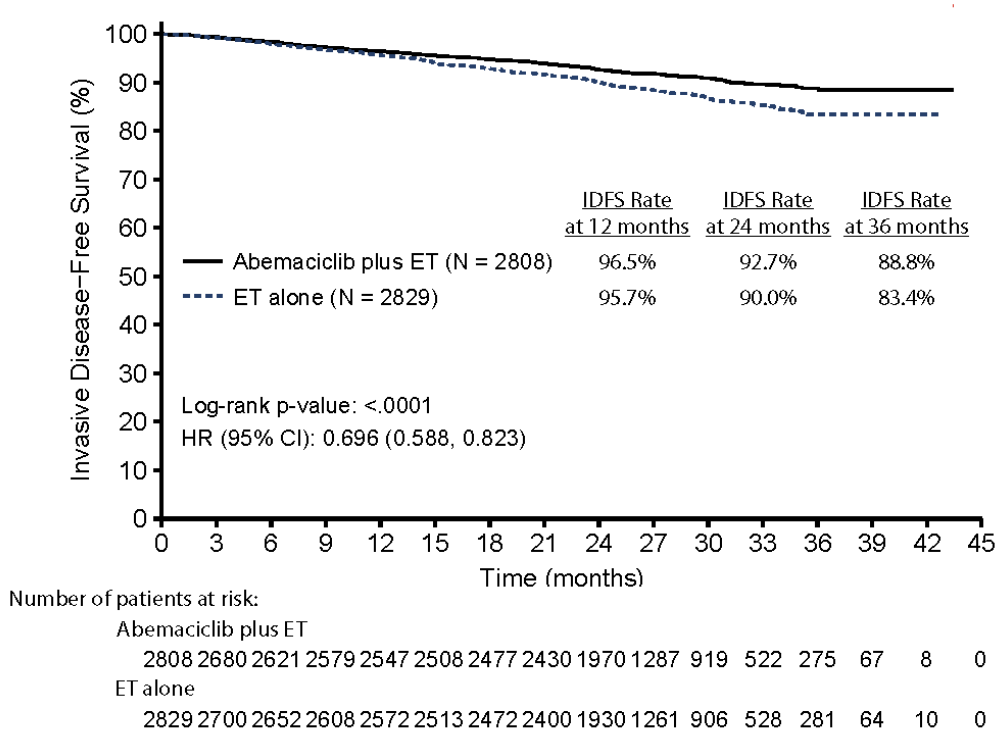
In a subsequent analysis (01 April 2021 cut-off), 90 % of the patients were off the 2-year study treatment period and the median duration of follow-up was approximately 27 months are summarised in Table 9b.

Table 9b. monarchE: Summary of efficacy data at final IDFS analysis (Intent-to-Treat Population)

	Yulareb plus endocrine therapy N = 2808	Endocrine therapy alone N = 2829
Invasive disease-free survival (IDFS)		
Number of patients with event (n, %)	232 (8.3)	333 (11.8)
Hazard ratio (95 % CI) and p-value	0.696 (0.588, 0.823), p = <.0001	
IDFS at 24 months (%, 95 % CI)	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)
Distant relapse free survival (DRFS)		
Number of patients with an event (n, %)	191 (6.8)	278 (9.8)
Hazard ratio (95 % CI)	0.687 (0.571, 0.826)	
DRFS at 24 months (%, 95 % CI)	94.1 (93.2, 95.0)	91.6 (90.5, 92.6)

Abbreviation: CI = confidence interval.

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



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

Advanced or Metastatic Breast Cancer

Randomised Phase 3 Study MONARCH 3: Yulareb in combination with aromatase inhibitors

The efficacy and safety of Yulareb in combination with an aromatase inhibitor (anastrozole or letrozole) was evaluated in MONARCH 3, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer who had not received prior systemic therapy in this disease setting. Patients were randomised in a 2:1 ratio to receive Yulareb 150 mg twice daily plus a non-steroidal aromatase inhibitor given daily at the recommended dose versus placebo plus a non-steroidal aromatase inhibitor according to the same schedule. The primary endpoint was

investigator-assessed progression-free survival (PFS) evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

The median age of patients enrolled was 63 years (range 32-88). Approximately 39 % of patients had received chemotherapy and 44 % had received antihormonal therapy in the (neo)adjuvant setting. Patients with prior (neo)adjuvant endocrine therapy must have completed this therapy at least 12 months before study randomisation. The majority of patients (96 %) had metastatic disease at baseline. Approximately 22 % of patients had bone-only disease, and 53 % patients had visceral metastases.

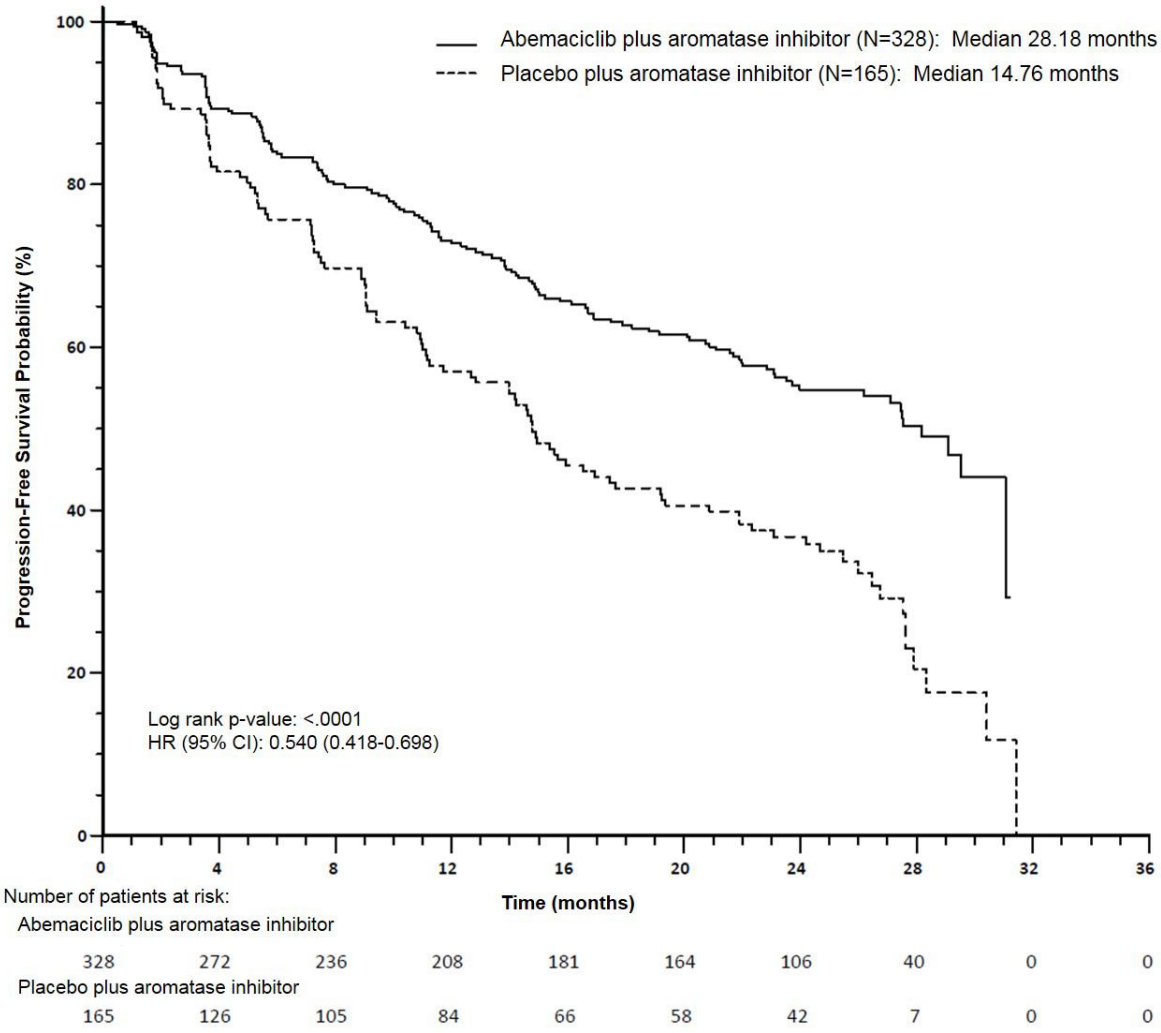
The study met its primary endpoint of improving PFS. Primary efficacy results are summarised in Table 10 and Figure 2.

Table 10. MONARCH 3: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	Yulareb plus aromatase inhibitor	**Placebo plus aromatase inhibitor**
Progression-free survival	**N=328**	**N=165**
Investigator assessment, number of events (%)	138 (42.1)	108 (65.5)
Median [months] (95% CI)	28.18 (23.51, NR)	14.76 (11.24, 19.20)
Hazard ratio (95% CI) and p-value	0.540 (0.418, 0.698), p = 0.000002	
Independent radiographic review, number of events (%)	91 (27.7)	73 (44.2)
Median [months] (95% CI)	NR (NR, NR)	19.36 (16.37, 27.91)
Hazard ratio (95% CI) and p-value	0.465 (0.339, 0.636); p < 0.000001	
Objective response rate[a] [%] (95% CI)	49.7 (44.3, 55.1)	37.0 (29.6, 44.3)
Duration of response [months] (95% CI)	27.39 (25.74, NR)	17.46 (11.21, 22.19)
Objective response for patients with measurable disease[a]	**N = 267**	**N = 132**
Objective response rate[b] [%] (95% CI)	61.0 (55.2, 66.9)	45.5 (37.0, 53.9)
Complete response, (%)	3.4	0
Partial response, (%)	57.7	45.5
Clinical benefit rate[c] (measurable disease) [%] (95% CI)	79.0 (74.1, 83.9)	69.7 (61.9, 77.5)

[a] Measurable disease defined per RECIST version 1.1
[b] Complete response + partial response
[c] Complete response + partial response + stable disease for ≥ 6 months
N=number of patients; CI=confidence interval; NR=not reached.

Figure 2: MONARCH 3: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



Progression-free survival (PFS) was significantly prolonged in the Yulareb plus aromatase inhibitor (AI) arm, (HR of 0.540 [95% CI: 0.418, 0.698]); median PFS was 28.18 months in the Yulareb plus AI arm and was 14.76 months in the placebo plus AI arm. These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 46 % for patients treated with abemaciclib plus an aromatase inhibitor.

Overall survival was not mature at the final PFS analysis (93 events observed across the two arms). The HR was 1.057 (95 % CI: 0.683, 1.633), p = 0.8017.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or ≥ 65 years), disease site, disease setting (de novo metastatic vs recurrent metastatic vs locally advanced recurrent), presence of measurable disease, progesterone receptor status, and baseline ECOG performance status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.567 [95% CI: 0.407, 0.789]), median PFS 21.6 months versus 14.0 months; in patients with bone-only disease (HR of 0.565 [95% CI: 0.306, 1.044]); and in patients with measurable disease (HR of 0.517 [95 % CI: 0.392, 0.681]).

Randomised Phase 3 Study MONARCH 2: Yulareb in combination with fulvestrant

The efficacy and safety of Yulareb in combination with fulvestrant was evaluated in MONARCH 2, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative

locally advanced or metastatic breast cancer. Patients were randomised in a 2:1 ratio to receive Yulareb 150 mg twice daily plus fulvestrant 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose, versus placebo plus fulvestrant according to the same schedule. The primary endpoint was investigator-assessed PFS evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

The median age of patients enrolled was 60 years (range, 32 - 91 years). In each treatment arm the majority of patients were white, and had not received chemotherapy for metastatic disease. 17 % of patients were pre/perimenopausal on ovarian suppression with a GnRH agonist. Approximately 56 % patients had visceral metastases. Approximately 25 % of patients had primary endocrine resistance (progression on endocrine therapy within the first 2 years of adjuvant endocrine therapy or within the first 6 months of first line endocrine therapy for metastatic breast cancer) and for the majority, endocrine resistance developed later. 59 % of patients had most recent endocrine therapy in the (neo)adjuvant setting, and 38 % in metastatic setting.

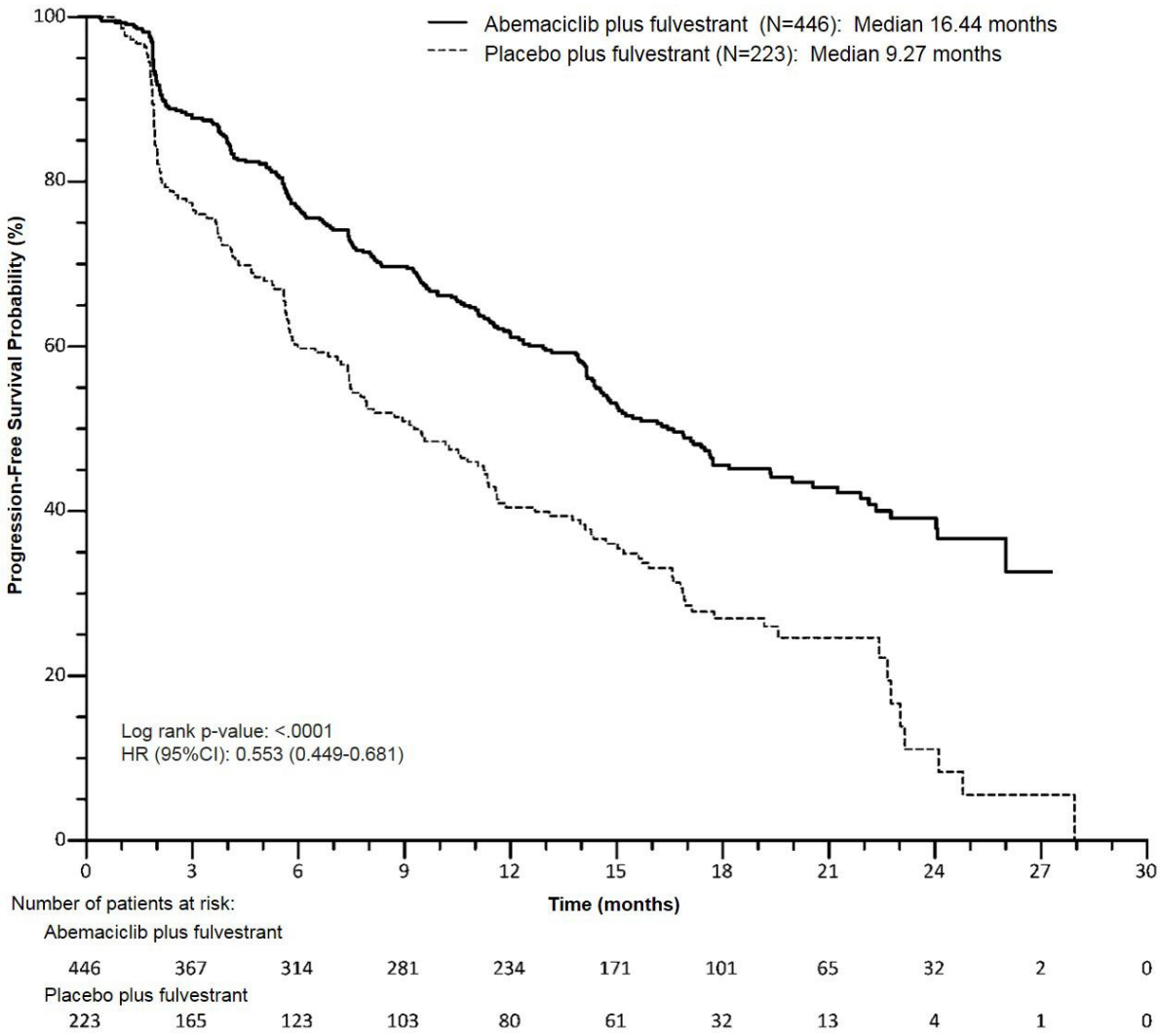
The study met its primary endpoint of improving PFS. Primary efficacy results are summarised in Table 11 and Figure 3.

Table 11. MONARCH 2: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	Yulareb plus fulvestrant	**Placebo plus fulvestrant**
Progression-free survival	**N = 446**	**N = 223**
Investigator assessment, number of events (%)	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) and p-value	0.553 (0.449, 0.681), p = 0.0000001	
Independent radiographic review, number of events (%)	164 (36.8)	124 (55.6)
Median [months] (95% CI)	22.4 (18.3, NR)	10.2 (5.8, 14.0)
Hazard ratio (95% CI) and p-value	0.460 (0.363, 0.584); p < 0.000001	
Objective response rate[a] [%] (95% CI)	35.2 (30.8, 39.6)	16.1 (11.3, 21.0)
Duration of response [months] (95% CI)	NR (18.05, NR)	25.6 (11.9, 25.6)
Objective response for patients with measurable disease[a]	**N = 318**	**N = 164**
Objective response rate[b] [%] (95% CI)	48.1 (42.6, 53.6)	21.3 (15.1, 27.6)
Complete response, (%)	3.5	0
Partial response, (%)	44.7	21.3
Clinical benefit rate[c] (measurable disease) [%] (95% CI)	73.3 (68.4, 78.1)	51.8 (44.2, 59.5)

[a] Measurable disease defined per RECIST version 1.1
[b] Complete response + partial response
[c] Complete response + partial response + stable disease for ≥ 6 months
N=number of patients; CI=confidence interval; NR=not reached.

Figure 3: MONARCH 2: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



Median PFS was significantly prolonged in the Yulareb plus fulvestrant arm (HR of 0.553 [95 % CI 0.449, 0.681]); median PFS was 16.4 months versus 9.3 months in the placebo plus fulvestrant arm. These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 44.7 % and a 7.2 month improvement in median PFS for patients treated with Yulareb plus fulvestrant. Yulareb plus fulvestrant prolonged progression-free survival with neither a clinically meaningful, or significant detriment to health-related quality of life.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, disease site, endocrine therapy resistance, presence of measurable disease, progesterone receptor status, and menopausal status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.481 [95% CI: 0.369, 0.627]), median PFS 14.7 months versus 6.5 months; in patients with bone-only disease (HR of 0.543 [95 % CI: 0.355, 0.833]); patients with measurable disease (HR of 0.523 [95 % CI: 0.412, 0.644]). In patients who were pre/perimenopausal, the hazard ratio was 0.415 (95 % CI: 0.246, 0.698); in patients who were progesterone receptor negative, the HR was 0.509 (95 % CI: 0.325, 0.797).

In a sub-population with locally advanced or metastatic disease that had not received prior endocrine therapy, the PFS was also consistent.

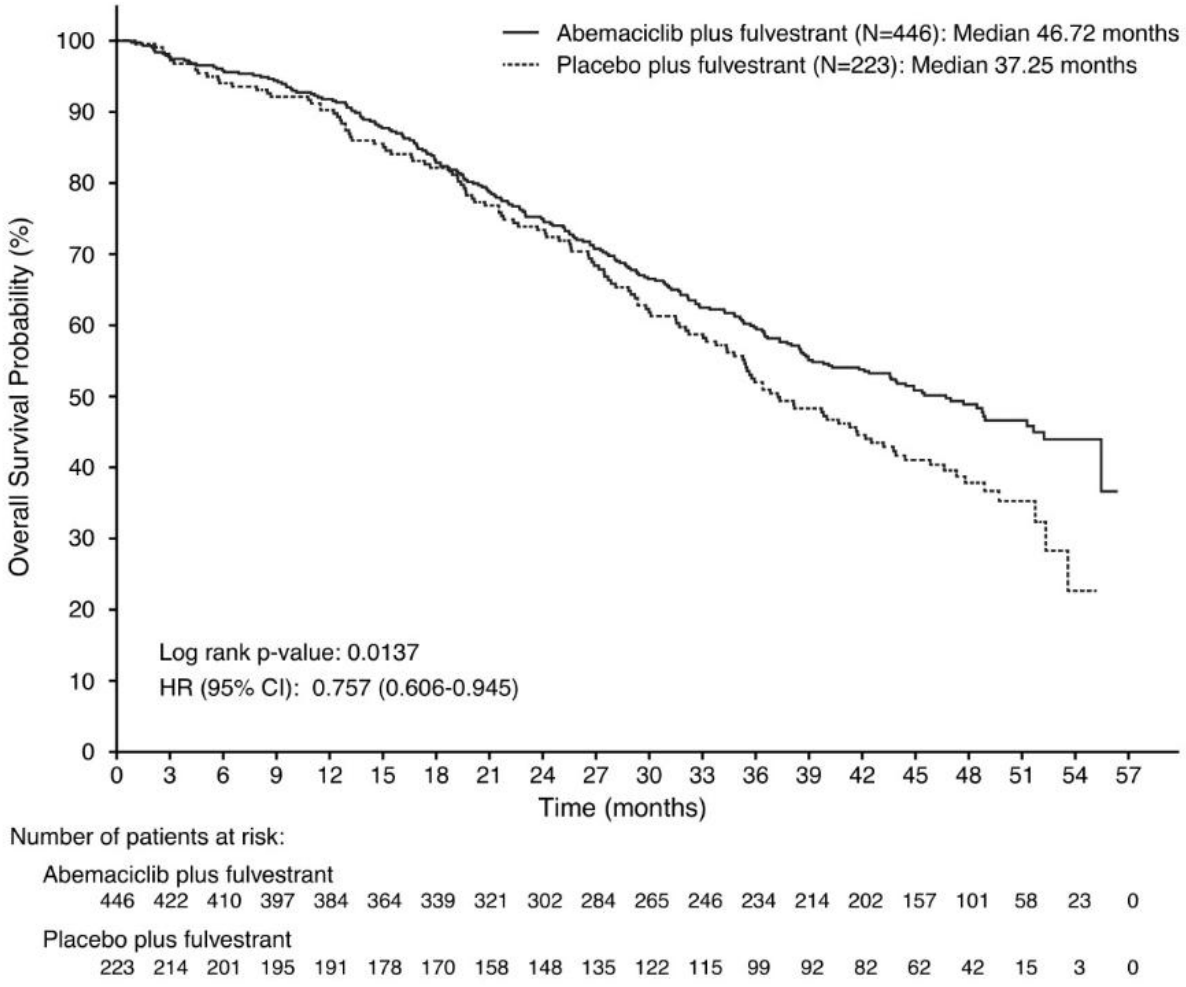
Overall survival (OS) analysis in the ITT population showed a statistically significant improvement in patients receiving Yularebs plus fulvestrant compared with those receiving placebo plus fulvestrant. The overall survival results are summarized in Table 12 and Figure 4.

Table 12. MONARCH 2: Summary of overall survival data (Intent-to-treat population)

	Yulareb plus fulvestrant	**Placebo plus fulvestrant**
Overall survival	N = 446	N = 223
Number of events (n, %)	211 (47.3)	127 (57.0)
Median OS [months] (95 % CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95 % CI)	0.757 (0.606, 0.945)	
p-value	0.0137	

N = number of patients; CI = confidence interval; OS = overall survival

Figure 4. MONARCH 2: Kaplan-Meier plot of overall survival (Intent-to-treat population)



Analyses for OS by stratification factors showed OS HR of 0.675 (95 % CI: 0.511, 0.891) in patients with visceral disease, and 0.686 (95 % CI: 0.451, 1.043) in patients with primary endocrine resistance.

5.2 Pharmacokinetic properties

Absorption

Abemaciclib absorption is slow, with a T_{max} of 8 hours and a mean absolute bioavailability of approximately 45 %. In the therapeutic dose range of 50 - 200 mg, the increase in plasma exposure (AUC) and C_{max} is approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and abemaciclib accumulated with a geometric mean accumulation ratio of 3.7 (58 % CV) and 5.8 (65 % CV) based on C_{max} and AUC, respectively. A high-fat meal increased combined AUC of abemaciclib and its active metabolites by 9% and increased C_{max} by 26 %. These changes were not considered to be clinically relevant. Therefore, abemaciclib can be taken with or without food.

Distribution

Abemaciclib is highly bound to plasma proteins in humans (mean bound fraction approximately 96 % to 98 %). The geometric mean systemic volume of distribution is approximately 750 L (69 % CV), indicating distribution of abemaciclib into tissues.

Concentrations of abemaciclib and its active metabolites in cerebrospinal fluid are comparable to unbound plasma concentrations.

Biotransformation

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolised to several metabolites primarily by cytochrome P450 (CYP) 3A4. The primary biotransformation is hydroxylation to a metabolite that circulates with an AUC that is 77 % of parent drug. In addition, N-desethyl and N-desethylhydroxy metabolites circulate at AUCs that are 39 % and 15 % of parent drug. These circulating metabolites are active with similar potency to abemaciclib.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib was 21.8 L/h (39.8 % CV), and the mean plasma elimination half-life for abemaciclib in patients was 24.8 hours (52.1 % CV). After a single oral dose of [^{14}C] -abemaciclib, approximately 81 % of the dose was excreted in faeces and 3.4 % excreted in urine. The majority of the dose eliminated in faeces was metabolites.

Special populations

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

Hepatic impairment
Abemaciclib is metabolised in the liver. Mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had no effect on the exposure of abemaciclib. In subjects with severe hepatic impairment (Child Pugh C), the $AUC_{0-\infty}$ of abemaciclib and potency adjusted unbound abemaciclib plus its active metabolites increased 2.1-fold and 2.4-fold, respectively. The half-life of abemaciclib increased from 24 to 55 hours (see section 4.2).

Renal impairment

Renal clearance of abemaciclib and its metabolites is minor. Mild and moderate renal impairment had no effect on the exposure of abemaciclib. There are no data in patients with severe renal impairment, end stage renal disease or in patients on dialysis.

5.3 Preclinical safety data

The primary target organ findings of potential relevance to humans include gastrointestinal and haematolymphopoietic organ effects in rats and dogs in studies up to 13 weeks duration. Effects in lung and skeletal muscle occurred only in rats at exposure levels approximately 2- fold higher than human exposure levels and effects in kidney occurred only in rats at exposure levels approximately 6- fold higher than human exposure levels. Complete or partial recovery was observed for all target organ at the end of the 28-day recovery period.

Genotoxicity

Abemaciclib was not mutagenic in a bacterial reverse mutation (Ames) assay, was not clastogenic in an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Specific animal studies to test abemaciclib for carcinogenic potential have not been performed.

Developmental toxicity

Abemaciclib was teratogenic and caused decreased foetal weight at maternal exposures similar to the recommended human dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

croscarmellose sodium
lactose monohydrate
microcrystalline cellulose
colloidal hydrated silica
sodium stearyl fumarate

Film coating

Yulareb 50 mg film-coated tablets
polyvinyl alcohol (E1203)
titanium dioxide (E171)
macrogol (E1521)
talc (E553b)
iron oxide yellow (E172)
iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7 PRESENTATION

Yulareb 50 mg, box of 2 blisters @ 7 tablets, Reg. No.:

HARUS DENGAN RESEP DOKTER

Manufactured by:
Lilly del Caribe, Inc.
12.6 KM 65th Infantry Road (PR01)
Carolina, Puerto Rico (PR) 00985
USA

Packed and released by:
Lilly S.A.
Avda. de la Industria, 30
28108 Alcobendas, Madrid

Spain

Registered by:
PT. Wigo Health Indonesia
Kabupaten Semarang, Indonesia

YULAREB
Yulareb 50 mg tablet salut selaput

Informasi Produk untuk Pasien

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mengkonsumsi obat ini karena leaflet ini berisi informasi yang penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali.
- Jika Anda mempunyai pertanyaan lebih lanjut, silakan bertanya kepada dokter, apoteker atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan diberikan kepada orang lain. Ini mungkin dapat membahayakan mereka, bahkan jika gejala-gejala dan penyakitnya sama dengan Anda.
- Jika Anda mengalami efek samping, beritahukan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping lain yang mungkin terjadi yang belum tercantum di leaflet ini. Silakan lihat bagian 4.

Apa isi leaflet ini

1. Apa Yulareb dan apa kegunaannya

Yulareb adalah obat kanker dengan kandungan zat aktif abemaciclib.

Abemaciclib menghambat fungsi dari protein yang disebut *cyclin-dependent kinase* 4 dan 6. Protein ini aktif secara tidak normal di beberapa sel kanker dan membuatnya tumbuh di luar kendali. Dengan menghambat aksi protein ini dapat memperlambat pertumbuhan sel kanker, mengecilkan tumor dan menunda perkembangan kanker.

Yulareb digunakan untuk mengobati kanker payudara jenis tertentu (*hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2(-)*) yang telah:

- menyebar ke kelenjar getah bening di ketiak tetapi tidak ke bagian tubuh lainnya dan memiliki karakteristik tertentu yang meningkatkan risiko kanker kembali. Pengobatan diberikan dalam kombinasi dengan terapi hormonal, seperti inhibitor aromatase atau tamoxifen, untuk mencegah kanker datang kembali setelah operasi (perawatan setelah operasi disebut terapi adjuvant).
  Risiko kekambuhan yang tinggi ditentukan oleh gambaran klinis dan patologis: baik ≥4 pALN (*positive axillary lymph nodes*), atau 1-3 pALN dan setidaknya salah satu dari kriteria berikut: ukuran tumor ≥5 cm atau tingkat histologis 3; atau 1-3 pALN dan indeks Ki-67 tinggi (≥20%).
- menyebar di luar tumor asli dan/atau ke organ lain. Diberikan bersama-sama dengan terapi hormon, seperti aromatase inhibitor atau fulvestrant.

2. Apa yang perlu Anda ketahui sebelum mengkonsumsi Yulareb

Jangan mengkonsumsi Yulareb
- jika Anda alergi terhadap abemaciclib atau kandungan lain dari obat ini (tercantum di bagian 6).

Peringatan dan perhatian
Yulareb dapat:

- menurunkan jumlah sel darah putih, dan Anda mungkin berisiko lebih besar terkena infeksi. Infeksi serius seperti infeksi paru-paru dapat mengancam jiwa;
- menyebabkan pembekuan darah di pembuluh darah;
- menyebabkan peradangan paru-paru yang parah atau mengancam jiwa;
- mempengaruhi cara kerja hati Anda;
- menyebabkan diare. Saat ada tanda pertama diare, mulailah pengobatan dengan antidiare, seperti loperamide. Minum banyak cairan.

Lihat bagian 4 "Efek samping yang mungkin terjadi", dan bicarakan dengan dokter Anda jika Anda mengalami gejala-gejala efek samping.

Apa saja yang akan dokter Anda periksa sebelum dan selama pengobatan
Anda akan menjalani tes darah rutin sebelum dan selama pengobatan untuk memeriksa apakah Yulareb mempengaruhi darah Anda (sel darah putih, sel darah merah, trombosit) atau konsentrasi enzim yang berasal dari hati dalam darah Anda.

Anak-anak dan remaja
Yulareb tidak untuk digunakan pada anak dan remaja dibawah 18 tahun.

Obat-obat lainnya dan Yulareb
Beritahukan dokter atau apoteker Anda jika Anda sedang, baru-baru ini menggunakan atau mungkin menggunakan obat lain.

Secara khusus, sebelum menggunakan Yulareb beritahukan dokter atau apoteker Anda jika Anda menggunakan:
- obat-obatan yang dapat meningkatkan konsentrasi Yulareb dalam darah:
  - **Clarithromycin** (antibiotik yang digunakan untuk mengobati infeksi bakteri)
  - **Itraconazole, ketoconazole, posaconazole, voriconazole** (digunakan untuk mengobati infeksi jamur)
  - **Lopinavir/ritonavir** (digunakan untuk mengobati HIV / AIDS)
  - **Digoxin** (digunakan untuk mengobati gangguan jantung)
  - **Dabigatran etexilate** (digunakan untuk mengurangi risiko stroke dan pembekuan darah)
- obat-obatan yang dapat mengurangi efektivitas Yulareb:
  - **Carbamazepine** (anti-epilepsi yang digunakan untuk mengobati *seizures* atau *fits*)
  - **Rifampicin**, digunakan untuk mengobati tuberkulosis (TB)
  - **Phenytoin** (digunakan untuk mengobati *seizures*)
  - **St. John's wort** (produk herbal yang digunakan untuk mengobati depresi ringan dan kecemasan)

Yulareb dengan makanan dan minuman
Hindari jus *grapefruit* atau *grapefruit* saat Anda minum obat ini karena dapat meningkatkan konsentrasi Yulareb dalam darah.

Kehamilan, menyusui dan kesuburan

Diskusikan kontrasepsi dengan dokter Anda jika ada kemungkinan Anda hamil. Jika Anda hamil, berpikir Anda mungkin sedang hamil atau berencana untuk memiliki bayi, mintalah saran dokter atau apoteker Anda sebelum menggunakan obat ini.

Kehamilan
Anda seharusnya tidak menggunakan Yulareb jika Anda sedang hamil.

Anda seharusnya menghindari menjadi hamil selama menggunakan Yulareb.

Jika Anda berpotensi memiliki anak, Anda harus menggunakan metode kontrasepsi yang memadai (misalnya, Kontrasepsi penghalang ganda seperti kondom dan diafragma) selama terapi dan setidaknya 3 minggu setelah menyelesaikan terapi.

Anda harus memberi tahu dokter Anda jika Anda hamil.

Menyusui
Anda seharusnya tidak menyusui selama menggunakan Yulareb. Tidak diketahui jika Yulareb bisa melewati Air Susu Ibu.

Mengemudi dan mengoperasikan mesin
Kelelahan dan pusing adalah efek samping yang sangat umum. Jika Anda merasa sangat lelah atau pusing, berhati-hatilah saat mengemudi atau menggoperasikan mesin.

Yulareb mengandung laktosa
Jika dokter mengatakan Anda memiliki intoleransi terhadap beberapa jenis gula, hubungi dokter Anda sebelum menggunakan obat ini.

Yulareb mengandung sodium (natrium)
Obat ini mengandung kurang dari 1 mmol natrium (23 gram) per tablet, pada dasarnya bisa dikatakan “bebas natrium”.

3. Bagaimana Anda mengkonsumsi Yulareb

Dosis yang direkomendasikan

Selalu gunakan obat ini tepat seperti yang dokter atau apoteker katakan kepada Anda. Konsultasikan dengan dokter atau apoteker jika Anda tidak yakin.

Ketika digunakan bersama dengan terapi endokrin untuk mengobati kanker payudara Anda, dosis Yulareb yang direkomendasikan adalah 150 mg diminum dua kali sehari.

Jika Anda mengalami efek samping tertentu saat Anda menggunakan Yulareb, dokter Anda dapat menurunkan dosis Anda atau menghentikan pengobatan sementara atau secara permanen.

Kapan dan bagaimana cara mengkonsumsi Yulareb

Minumlah Yulareb dua kali sehari, pada saat yang sama setiap harinya, lebih baik di pagi dan malam, sehingga ada cukup obat dalam tubuh Anda sepanjang waktu.

Anda dapat meminum tablet baik dengan atau tanpa makanan, hindari *grapefruit* dan jus *grapefruit* (lihat bagian 2 “Yulareb dengan makanan dan minuman”).

Telan tablet seutuhnya dengan segelas air. Jangan mengunyah, menghancurkan atau membelah tablet sebelum menelan.

Berapa lama penggunaan Yulareb
Gunakan Yulareb secara rutin selama yang dikatakan dokter Anda. Jika Anda menggunakan Yulareb untuk pengobatan adjuvan, Anda harus meminumnya hingga 2 tahun atau sampai penyakit kambuh atau toksisitas yang tidak dapat diterima terjadi.

Jika Anda mengkonsumsi Yulareb melebihi yang seharusnya
Jika Anda mengkonsumsi terlalu banyak tablet, atau jika seseorang mengambil obat Anda, hubungi dokter atau rumah sakit untuk meminta saran. Perlihatkan dus Yulareb dan brosur ini. Perawatan medis mungkin diperlukan.

Jika Anda lupa mengkonsumsi Yulareb
Jika Anda muntah setelah mengkonsumsi atau lupa meminum dosis obat, minumlah dosis selanjutnya seperti waktu yang biasa. Jangan minum dosis ganda untuk mengganti dosis yang terlupakan atau dimuntahkan.

Jika Anda berhenti mengkonsumsi Yulareb
Jangan berhenti mengkonsumsi Yulareb kecuali dikatakan oleh dokter Anda.

Jika Anda mempunyai pertanyaan lebih lanjut terkait penggunaan obat ini, tanyakan ke dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya. Beritahukan dokter Anda segera jika Anda mengalami salah satu efek samping berikut:

- Gejala seperti menggigil atau demam. Ini bisa menjadi tanda jumlah sel darah putih yang rendah (yang dapat mempengaruhi lebih dari 1 diantara 10 orang) dan harus segera diobati. Jika Anda menderita batuk, demam, dan kesulitan bernapas, atau nyeri dada, ini bisa menjadi tanda infeksi paru-paru. Infeksi serius atau yang mengancam jiwa jarang terjadi (dapat mempengaruhi hingga 1 diantara 100 orang).
- Kaki bengkak yang nyeri, nyeri dada, sesak napas, napas cepat atau detak jantung yang cepat karena hal ini bisa saja merupakantanda-tanda pembekuan darah di pembuluh darah (yang dapat mempengaruhi hingga 1 diantara 10 orang).
- Diare (yang dapat mempengaruhi lebih dari 1 diantara 10 orang).

Lihat Bagian 2 untuk informasi lebih lanjut tentang salah satu efek yang mungkin tercantum di atas.

Efek samping lain Yulareb termasuk:
Efek samping yang sangat umum terjadi (dapat mempengaruhi lebih dari 1 diantara 10 orang)

- Infeksi
- Penurunan sel darah putih, sel darah merah, dan trombosit darah
- Mual (merasa sakit), muntah
- Peradangan atau luka di dalam mulut
- Nafsu makan menurun

- Sakit kepala
- Perubahan indera perasa
- Rambut rontok
- Kelelahan
- Pusing
- Gatal
- Ruam
- Kelainan pada tes fungsi hati dalam darah

Efek samping yang umum terjadi (dapat mempengaruhi pada 1 diantara 10 orang)
- Mata berair
- Kelemahan otot
- Kulit kering
- Peradangan pada paru-paru yang menyebabkan sesak nafas, batuk dan peningkatan suhu
- Gangguan pada pencernaan atau sakit perut
- Gangguan pada kuku seperti kuku patah atau terbelah

Pelaporan efek samping
Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini. Anda dapat juga melaporkan keluhan efek samping atau konsisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut: Telepon: +62 21 21684084 atau Email: IDsafety@zuelligpharma.com. Dengan melaporkan efek samping Anda dapat membantu menyediakan informasi keamanan lebih lanjut dari obat ini.

5. Bagaimana cara menyimpan Yulareb

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum di blister dan karton luar setelah EXP. Tanggal kadaluarsa merujuk pada hari terakhir di bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan gunakan obat ini jika kemasan rusak atau ada tanda-tanda kerusakan.

Jangan buang obat ini melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat-obatan yang tidak digunakan. Cara ini dapat membantu untuk melindungi lingkungan.

6. Isi dari kemasan dan informasi lainnya

Apa isi Yulareb
- Zat aktifnya adalam abemaciclib. Yulareb tablet salut selaput tesedia dalam beberapa sediaan:
  - Yulareb 50 mg tablet salut selaput: setiap tablet mengandung 50 mg abemaciclib

- Zat tambahan lainnya dalam obat ini adalah:

- Tablet inti: *colloidal hydrated silica, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate*
- Salut selaput: *titanium dioxide (E171), talc (E553b), polyvinyl alcohol (E1203), macrogol 3350 (E1521), iron oxide yellow (E172) , iron oxide red (E172).*

Seperti apa rupa Yulareb dan isi kemasannya

- Yulareb 50 mg tablet salut selaput berwarna krem, tablet oval dengan logo “Lilly” pada satu sisi dan “50” pada sisi lainnya.

Yulareb 50 mg, dus isi 2 blister @ 7 tablet salut selaput, Reg. No.:

HARUS DENGAN RESEP DOKTER

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