

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KISQALI FEMARA CO-PACK safely and effectively. See full prescribing information for KISQALI FEMARA CO-PACK.

**KISQALI® FEMARA® CO-PACK (ribociclib tablets; letrozole tablets), co-packaged for oral use**

**Initial U.S. Approval: 2017**

### RECENT MAJOR CHANGES

Indications and Usage (1.1)	9/2024
Dosage and Administration (2.1, 2.2)	9/2024
Warnings and Precautions (5.1, 5.3, 5.4, 5.5)	9/2024

### INDICATIONS AND USAGE

KISQALI FEMARA CO-PACK, a co-packaged product containing ribociclib, a kinase inhibitor, and letrozole, an aromatase inhibitor, is indicated:

- for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence. (1)
- as initial endocrine-based therapy for the treatment of adults with HR-positive, HER2-negative advanced or metastatic breast cancer therapy. (1)

### DOSAGE AND ADMINISTRATION

KISQALI FEMARA CO-PACK tablets are taken in combination orally with or without food. (2)

#### Early Breast Cancer

- KISQALI recommended starting dose: 400 mg orally (two 200 mg tablets) taken once daily for 21 consecutive days followed by 7 days off KISQALI treatment. (2.1)

#### Advanced or Metastatic Breast Cancer

- KISQALI recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily for 21 consecutive days followed by 7 days off KISQALI treatment. (2.1)

KISQALI dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability. (2.2)

FEMARA: 2.5 mg (one tablet) continuously for a 28-day cycle. (2.1)

### DOSAGE FORMS AND STRENGTHS

Tablets:

- KISQALI: 200 mg (3)
- FEMARA: 2.5 mg (3)

### CONTRAINDICATIONS

Known hypersensitivity to letrozole, or to any excipients of FEMARA. (4)

### WARNINGS AND PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis: Patients treated with CDK 4/6 inhibitors should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Interrupt and evaluate patients with new or worsening respiratory symptoms suspected to be due to ILD/pneumonitis. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis. (2.2, 5.1)
- Severe Cutaneous Adverse Reactions (SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur with KISQALI treatment. Permanently discontinue KISQALI in patients with SCARs or other life-threatening cutaneous reactions. (2.2, 5.2)
- QT Interval Prolongation: Monitor electrocardiograms (ECGs) and electrolytes prior to initiation of treatment with KISQALI. Repeat ECGs at

approximately Day 14 of the first cycle, and as clinically indicated.

Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated. Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors. (2.2, 5.3, 7.1, 7.4)

- Hepatobiliary Toxicity: Increases in serum transaminase and bilirubin levels have been observed. Perform liver function tests (LFTs) before initiating treatment with KISQALI FEMARA CO-PACK. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. (2.2, 5.4)
- Neutropenia: Perform complete blood count (CBC) before initiating therapy with KISQALI FEMARA CO-PACK. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. (2.2, 5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm when administered to pregnant women. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during therapy. (5.6, 8.1, 8.3)

### ADVERSE REACTIONS

- In patients with early breast cancer, the most common (incidence  $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, are lymphocytes decreased, leukocytes decreased, neutrophils decreased, hemoglobin decreased, alanine aminotransferase increased, aspartate aminotransferase increased, infections, creatinine increased, platelets decreased, headache, nausea, and fatigue. (6)
- In patients with advanced or metastatic breast cancer, the most common (incidence  $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, are leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, alanine aminotransferase increased, aspartate aminotransferase increased, infections, nausea, fatigue, platelets decreased, diarrhea, headache, alopecia, vomiting, back pain, constipation, cough, rash, creatinine increased, and abdominal pain. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- CYP3A4 Inhibitors: Avoid concomitant use of KISQALI FEMARA CO-PACK with strong CYP3A inhibitors. If strong inhibitors cannot be avoided, reduce KISQALI dose. (2.2, 7.1)
- CYP3A4 Inducers: Avoid concomitant use of KISQALI FEMARA CO-PACK with strong CYP3A inducers. (7.2)
- CYP3A Substrates: The dose of CYP3A substrates with narrow therapeutic indices may need to be reduced when given concurrently with KISQALI FEMARA CO-PACK. (7.3)
- Drugs Known to Prolong QT Interval: Avoid concomitant use of drugs known to prolong QT interval, such as anti-arrhythmic medicines. (7.4)

### USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 9/2025**

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Early Breast Cancer

KISQALI® FEMARA® CO-PACK is indicated for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.

#### 1.2 Advanced or Metastatic Breast Cancer

KISQALI® FEMARA® CO-PACK indicated as initial endocrine-based therapy for the treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

##### Important Administration Instructions

The KISQALI FEMARA CO-PACK is comprised of ribociclib tablets co-packaged with letrozole tablets, to provide a 28-day treatment regimen. KISQALI FEMARA CO-PACK can be taken with or without food [*see Clinical Pharmacology (12.3)*].

Pre/perimenopausal women, or men, treated with KISQALI FEMARA CO-PACK should be treated with a luteinizing hormone-releasing hormone (LHRH) agonist according to current clinical practice standards.

Patients should take their doses of KISQALI FEMARA CO-PACK at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time. Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

##### Early Breast Cancer

- **KISQALI:** The recommended dosage of KISQALI is 400 mg (two 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles.
- **FEMARA:** 2.5 mg (one tablet) taken once daily throughout the 28-day cycle.

In patients with early breast cancer, treatment with KISQALI should continue for 3 years or until disease recurrence or unacceptable toxicity occurs.

##### Advanced or Metastatic Breast Cancer

- **KISQALI:** The recommended dosage for KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles.
- **FEMARA:** 2.5 mg (one tablet) taken once daily throughout the 28-day cycle.

Refer to the Full Prescribing Information for the recommended dosage for each product.

#### 2.2 Dose Modifications

##### Dose Modifications for Adverse Reactions

The recommended dose modifications of KISQALI for adverse reactions are listed in Table 1.

Dose modifications are not recommended for FEMARA when administered with KISQALI for the adverse reactions of KISQALI, including neutropenia, hepatobiliary toxicity, or QT prolongation [*see Dosage and Administration (2)*].

**Table 1: Recommended Dose Modification of KISQALI FEMARA CO-PACK for Adverse Reactions**

Level	KISQALI		FEMARA	
	Dose	Number of tablets	Dose	Number of tablets
<b>Early breast cancer</b>				
Starting dose	400 mg/day	two 200 mg tablets	2.5 mg/day	one 2.5 mg tablet
Dose reduction	200 mg/day*	one 200 mg tablet	2.5 mg/day	one 2.5 mg tablet
<b>Advanced or metastatic breast cancer</b>				
Starting dose	600 mg/day	three 200 mg tablets	2.5 mg/day	one 2.5 mg tablet
First dose reduction	400 mg/day	two 200 mg tablets	2.5 mg/day	one 2.5 mg tablet
Second dose reduction	200 mg/day*	one 200 mg tablet	2.5 mg/day	one 2.5 mg tablet

\*If dose reduction below 200 mg/day is required, discontinue KISQALI.

Tables 2, 3, 4, 5, 6, and 7 summarize recommendations for dose interruption, reduction, or discontinuation of KISQALI in the management of specific adverse reactions. Dose modification of KISQALI FEMARA CO-PACK is recommended based on individual patient safety and tolerability.

**Table 2: Dose Modification and Management for Interstitial Lung Disease/Pneumonitis**

	<b>Grade 1 (asymptomatic)</b>	<b>Grade 2 (symptomatic)</b>	<b>Grade 3 (severe symptomatic) or 4 (life-threatening)</b>
<b>ILD/Pneumonitis</b> <i>[see Warnings and Precautions (5.1)]</i>	No dose interruption or adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to Grade $\leq$ 1 then consider resuming KISQALI at the next lower dose level*. If Grade 2 recurs, discontinue KISQALI.	Discontinue KISQALI.

Abbreviation: ILD, interstitial lung disease.

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

\*An individualized benefit-risk assessment should be performed when considering resuming KISQALI.

**Table 3: Dose Modification and Management for Cutaneous Adverse Reactions, Including SCARs**

	<b>Grade 1</b> ( $< 10\%$ body surface area (BSA) with active skin toxicity, no signs of systemic involvement)	<b>Grade 2</b> ( $10\%-30\%$ BSA with active skin toxicity, no signs of systemic involvement)	<b>Grade 3</b> (severe rash not responsive to medical management; $> 30\%$ BSA with active skin toxicity, signs of systemic involvement present; SJS*)	<b>Grade 4</b> (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life threatening consequences; TEN**)
	No dose adjustment is required.  Initiate appropriate medical therapy and monitor as clinically indicated.		Interrupt KISQALI until the etiology of the reaction has been determined.  If the etiology is a SCAR, permanently discontinue KISQALI.  If the etiology is not a SCAR, interrupt dose until recovery to Grade $\leq 1$ , then resume KISQALI at same dose level.  If the cutaneous adverse reaction still recurs at Grade 3, resume KISQALI at the next lower dose level.	Permanently discontinue KISQALI.

Abbreviations: BSA, body surface area; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

\*SJS (Grade 3 and 4) is defined as skin sloughing covering  $< 10\%$  BSA and  $10\%-30\%$  BSA, respectively, with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment).

\*\*TEN (Grade 4) is defined as skin sloughing covering  $\geq 30\%$  BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment).

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

**Table 4: Dose Modification and Management of KISQALI for QT Prolongation**

<b>QTcF* prolongation</b>	<b>Early breast cancer</b>	<b>Advanced or metastatic breast cancer</b>
<b><math>&gt; 480</math> ms and <math>\leq 500</math> ms</b>	Interrupt KISQALI treatment and wait until QTcF resolves to $\leq 480$ ms	
	Resume at the same dose	Reduce to the next lower dose level
	If QTcF $> 480$ ms recurs, interrupt KISQALI treatment and wait until QTcF resolves to $\leq 480$ ms, then resume at next lower dose level.	
<b><math>&gt; 500</math> ms</b>	Interrupt KISQALI treatment and wait until QTcF resolves to $\leq 480$ ms, then resume at next lower dose level.  If QTcF $> 500$ ms recurs, discontinue KISQALI.	

Permanently discontinue KISQALI if QTcF interval prolongation is either  $> 500$  ms or  $> 60$  ms change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, syncope, or signs/symptoms of serious arrhythmia.

*Note:* If dose reduction below 200 mg/day is required, discontinue KISQALI.  
 Electrocardiograms (ECGs) should be assessed prior to initiation of treatment in all patients.  
 Repeat ECGs at approximately Day 14 of the first cycle, and as clinically indicated.  
 In case of QTcF prolongation at any given time during treatment, monitor ECG more frequently, and as clinically indicated.  
 \*QTcF = QT interval corrected by Fridericia's formula.

**Table 5: Dose Modification and Management of KISQALI for Hepatobiliary Toxicity**

	<b>Grade 1</b> ( <b>&gt; ULN – 3 x ULN</b> )	<b>Grade 2</b> ( <b>&gt; 3 to 5 x ULN</b> )	<b>Grade 3</b> ( <b>&gt; 5 to 20 x ULN</b> )	<b>Grade 4</b> ( <b>&gt; 20 x ULN</b> )
<b>AST and/or ALT elevations from baseline*, WITHOUT increase in total bilirubin above 2 x ULN</b> <i>[see Warnings and Precautions (5.4)]</i>	No dose adjustment is required.	<u>Baseline* at &lt; Grade 2:</u> Dose interruption until recovery to ≤ baseline grade, and then resume KISQALI at same dose level. If Grade 2 recurs, resume KISQALI at next lower dose level.  ----- <u>Baseline* at Grade 2:</u> No dose interruption.	Dose interruption until recovery to ≤ baseline* grade, and then resume at next lower dose level.  If Grade 3 recurs, discontinue KISQALI.	Discontinue KISQALI.
<b>Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis</b> <i>[see Warnings and Precautions (5.4)]</i>	If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2 x ULN irrespective of baseline grade, discontinue KISQALI.			

Perform Liver Function Tests (LFTs) before initiating treatment with KISQALI.  
 Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.  
 If Grade ≥ 2 abnormalities are noted, monitor more frequently, and as clinically indicated.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.  
 \*Baseline = prior to treatment initiation.  
 Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

**Table 6: Dose Modification and Management of KISQALI for Neutropenia**

	<b>Grade 1 or 2</b> (ANC 1000/mm <sup>3</sup> – < LLN)	<b>Grade 3</b> (ANC 500 - < 1000/mm <sup>3</sup> )	<b>Grade 3 Febrile* Neutropenia</b>	<b>Grade 4</b> (ANC < 500/mm <sup>3</sup> )
<b>Neutropenia</b> <i>[see Warnings and Precautions (5.5)]</i>	No dose adjustment is required.	Dose interruption until recovery to Grade ≤ 2. Resume KISQALI at the same dose level. If toxicity recurs at Grade 3, dose interruption until recovery, then resume KISQALI at the next lower dose level.	Dose interruption until recovery of neutropenia to Grade ≤ 2. Resume KISQALI at the next lower dose level.	Dose interruption until recovery to Grade ≤ 2. Resume KISQALI at the next lower dose level.
Perform complete blood counts (CBCs) before initiating treatment with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.				
Abbreviations: ANC, absolute neutrophil count; LLN, lower limit of normal. *Grade 3 neutropenia with single episode of fever > 38.3°C (or) 38°C or above for more than one hour and/or concurrent infection. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.				

**Table 7: Dose Modification and Management of KISQALI for Other Toxicities\***

	<b>Grade 1 or 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Other toxicities</b>	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to Grade ≤ 1 then resume KISQALI at same dose level. If Grade 3 recurs, resume KISQALI at the next lower dose level.	Discontinue KISQALI.
*Excluding interstitial lung disease (ILD)/pneumonitis, cutaneous adverse reactions, including severe cutaneous adverse reactions (SCARs), QT interval prolongation, hepatobiliary toxicity, and neutropenia. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.			

Refer to the Full Prescribing Information for the coadministered aromatase inhibitor for dose modification guidelines in the event of toxicity and other relevant safety information.

#### Dose Modification for Use with Strong CYP3A Inhibitors

Avoid concomitant use of KISQALI FEMARA CO-PACK with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhibition *[see Drug Interactions (7.1)]*.

If a strong CYP3A inhibitor must be coadministered, reduce the KISQALI dose as shown in Table 8

**Table 8: Dose Modification for Use with Strong CYP3A Inhibitors**

<b>Indication</b>	<b>Co-administration with Strong CYP3A Inhibitors</b>
<b>Early breast cancer</b>	Reduce the KISQALI dose to 200 mg once daily.
<b>Advanced or metastatic breast cancer</b>	Reduce the KISQALI dose to 400 mg once daily.

If the strong inhibitor is discontinued, change the KISQALI dose (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

#### Dose Modification for Hepatic Impairment

The recommended dose modifications for patients with hepatic impairment are shown in Table 9 [see *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

**Table 9: Dose Modification for Hepatic Impairment**

Indication	Mild hepatic impairment (Child-Pugh class A)	Moderate and severe hepatic impairment (Child-Pugh class B or C)
Early breast cancer	No dose adjustment is necessary	No dose adjustment is necessary
Advanced or metastatic breast cancer	No dose adjustment is necessary	KISQALI 400 mg once daily

The dose of FEMARA in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50% [see *Clinical Pharmacology (12.3)*]. The recommended dose of FEMARA for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on FEMARA exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined [see *Clinical Pharmacology (12.3)*]. Review the Full Prescribing Information for the coadministered aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

#### Dose Modification for Renal Impairment

The recommended starting dose is 200 mg KISQALI once daily for patients with severe renal impairment [see *Use in Specific Populations (8.7)*, *Clinical Pharmacology (12.3)*].

No dosage adjustment of FEMARA is required for patients with renal impairment if creatinine clearance is greater than or equal to 10 mL/min [see *Clinical Pharmacology (12.3)*].

### **3 DOSAGE FORMS AND STRENGTHS**

KISQALI FEMARA CO-PACK is KISQALI (ribociclib) tablets co-packaged with FEMARA (letrozole) tablets.

- Tablet: 200 mg ribociclib (equivalent to 254.40 mg ribociclib succinate).  
Film-coated, light greyish violet, round, curved with beveled edges, debossed with “RIC” on one side and “NVR” on the other side.
- Tablet: 2.5 mg letrozole.  
Dark yellow, film-coated, round, slightly biconvex, with beveled edges (imprinted with the letters “FV” on one side and “CG” on the other side).

### **4 CONTRAINDICATIONS**

Known hypersensitivity to the active substance (letrozole), or to any of the excipients of FEMARA. Refer to FEMARA Prescribing Information.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Interstitial Lung Disease/Pneumonitis**

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

In patients with early breast cancer (NATALEE) who received 400 mg KISQALI plus a non-steroidal aromatase inhibitor (NSAI), 1.5% of patients had ILD/pneumonitis (Grade 1-2).

In patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-7), 1.2% of KISQALI-treated patients had ILD/pneumonitis (any grade, 0.3% had Grade 3-4). Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death [see *Adverse Reactions (6.2)*].



Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis [see *Dosage and Administration* (2.2)]. Refer to the Full Prescribing Information for KISQALI®.

## 5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), can occur in patients treated with KISQALI [see *Adverse Reactions* (6.2)].

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined [see *Dosage and Administration* (2.2)]. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs during KISQALI treatment.

## 5.3 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner [see *Clinical Pharmacology* (12.2)].

Avoid KISQALI in patients who are at significant risk of developing Torsades de Pointes (TdP), including those with:

- congenital long QT syndrome;
- uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism;
- electrolyte abnormalities;
- taking drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 [see *Dosage and Administration* (2.2), *Drug Interactions* (7.4)].

In patients with early breast cancer (NATALEE) who received 400 mg KISQALI plus NSAI, 8 out of 2494 patients (0.3%) had > 500 ms post-baseline QTcF interval value and 50 out of 2494 patients (2%) had > 60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first four weeks of KISQALI. There were no reported cases of Torsades de Pointes.

In patients with advanced or metastatic breast cancer (MONALEESA-2 and MONALEESA-7) who received 600 mg KISQALI plus NSAI, 7 out of 574 patients (1%) had a > 500 ms post-baseline QTcF value, and 29 out of 574 patients (5%) had a > 60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first four weeks of KISQALI. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, in the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 [see *Adverse Reactions* (6)].

Perform ECG in all patients prior to starting KISQALI FEMARA CO-PACK. Initiate treatment with KISQALI FEMARA CO-PACK only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous, and magnesium) prior to the initiation of KISQALI FEMARA CO-PACK, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI FEMARA CO-PACK [see *Dosage and Administration* (2.2)].

## 5.4 Hepatobiliary Toxicity

In patients with early and advanced or metastatic breast cancer, drug-induced liver injury and increases in transaminases occurred with KISQALI.

In patients with early breast cancer (NATALEE) treated with KISQALI, drug-induced liver injury was reported in 9 patients (0.4%), of which 5 were Grade  $\geq 3$ , and 8 had resolved as of the data cutoff. There were 8 (0.3%) clinically confirmed Hy's Law cases (including 4 out of 9 drug-induced liver injury mentioned above), 6 of which had resolved within 303 days and 2 of which were improving, all after discontinuation of KISQALI. Grade 3 or 4 increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred in 8% and 4.7% respectively; including Grade 4 increases in ALT (1.5%) and AST (0.8%).

In patients with advanced or metastatic breast cancer (MONALEESA-2 and MONALEESA-7), treated with KISQALI Grade 3 or 4 increases in ALT and AST occurred in 11% and 8%, respectively.

Among the patients who had Grade  $\geq 3$  ALT/AST elevation, the median time-to-onset was 111 days for the KISQALI plus aromatase inhibitor treatment arm. The median time to resolution to Grade  $\leq 2$  was 22 days in the KISQALI plus aromatase inhibitor treatment arm. In MONALEESA-2, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 4 (1%) patients and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) in all patients before initiating KISQALI FEMARA CO-PACK. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated [*see Dosage and Administration (2.2)*].

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobiliary Toxicity) [*see Dosage and Administration (2.2)*].

## 5.5 Neutropenia

KISQALI causes concentration-dependent neutropenia.

In patients with early breast cancer (NATALEE) who received KISQALI plus NSAI, 94%, including 45% of Grade 3 or 4, had a decrease in neutrophil counts (based on laboratory findings), 63% had an adverse reaction of neutropenia, and 0.3% had febrile neutropenia. The median time to Grade  $\geq 2$  neutropenia was 18 days. The median time to resolution of Grade  $\geq 3$  neutropenia to Grade  $< 3$  was 10 days. Treatment discontinuation due to neutropenia was required in 1.1% of patients.

In patients with advanced or metastatic breast cancer (MONALEESA-2 and MONALEESA-7), who received KISQALI plus NSAI, 79% had neutropenia, 66% had Grade 3 or 4 decrease in neutrophil count (based on laboratory findings), and 2% had febrile neutropenia. The median time to Grade  $\geq 2$  neutropenia was 16 days. The median time to resolution of Grade  $\geq 3$  neutropenia to Grade  $< 3$  was 15 days. Treatment discontinuation due to neutropenia was required in 1% of patients.

Perform a complete blood count (CBC) in all patients before initiating KISQALI FEMARA CO-PACK. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6 [*see Dosage and Administration (2.2)*].

## 5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI FEMARA CO-PACK can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Letrozole caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI FEMARA CO-PACK and for at least 3 weeks after the last dose [*see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*].

## 6 ADVERSE REACTIONS

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

- Interstitial Lung Disease/Pneumonitis [*see Warnings and Precautions (5.1)*]
- Severe Cutaneous Adverse Reactions [*see Warnings and Precautions (5.2)*]
- QT Interval Prolongation [*see Warnings and Precautions (5.3)*]
- Hepatobiliary Toxicity [*see Warnings and Precautions (5.4)*]
- Neutropenia [*see Warnings and Precautions (5.5)*]

### 6.1 Clinical Trials 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.

The data described in WARNINGS AND PRECAUTIONS reflect exposure to KISQALI plus non-steroidal aromatase inhibitor (NSAI) in 2526 patients with early breast cancer (NATALEE), of whom 51% completed 36 months of KISQALI treatment. The most common ( $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, were lymphocytes decreased (97%), leukocytes decreased (95%), neutrophils decreased (94%), hemoglobin decreased (47%), alanine aminotransferase increased (45%), aspartate aminotransferase increased (44%), infections (37%), creatinine increased (33%), platelets decreased (28%), headache (23%), nausea (23%), and fatigue (22%).

In additions, the pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to KISQALI in 582 patients with advanced or metastatic breast cancer (MONALEESA-2 and MONALEESA-7), of whom 80% were exposed for 6 months or longer and 65% were exposed for greater than one year. The most common ( $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, were leukocytes decreased (94%), neutrophils decreased (94%), hemoglobin decreased (72%), lymphocytes decreased (59%), alanine aminotransferase increased (53%), aspartate aminotransferase increased (53%), infections (46%), nausea (46%), fatigue (36%), platelets decreased (34%), diarrhea (33%), headache (29%), alopecia (29%), vomiting (29%), back pain (25%), constipation (25%), cough (24%), rash (22%), creatinine increased (20%), and abdominal pain (20%).

#### NATALEE: KISQALI in Combination with a Non-steroidal Aromatase Inhibitor as Adjuvant Treatment

##### *Adults with HR-positive, HER2-negative Stage II and III Early Breast Cancer at High Risk of Recurrence*

The safety of KISQALI was evaluated in NATALEE, a clinical trial of 5101 patients who received KISQALI plus NSAI or NSAI alone, with or without goserelin [*see Clinical Studies (14)*]. The median duration of exposure to KISQALI was 33 months.

Serious adverse reactions occurred in 14% of patients who received KISQALI. Serious adverse reactions in  $> 0.5\%$  of patients who received KISQALI included COVID-19 (1.1%), pneumonia (0.8%), and pulmonary embolism (0.6%).

Fatal adverse reactions occurred in 0.6% of patients who received KISQALI. Fatal adverse reactions in  $\geq 0.1\%$  of patients receiving KISQALI included COVID-19 or COVID-19 pneumonia (0.2%) and pulmonary embolism (0.1%).

Permanent discontinuation of KISQALI due to an adverse reaction occurred in 20% of patients. Adverse reactions which resulted in permanent discontinuation of KISQALI in  $\geq 2\%$  of patients were alanine aminotransferase or aspartate aminotransferase increased (8%).

Dosage interruptions of both KISQALI plus NSAI due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in  $\geq 5\%$  of patients included neutropenia or neutrophil count decreased (43%), alanine aminotransferase or aspartate aminotransferase increased (11%), COVID-19 (10%), and hypomagnesemia (5%).

Dose reductions of KISQALI due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dose reductions in  $\geq 2\%$  of patients included neutropenia or neutrophil count decreased (14%) and liver function abnormal (2.3%).

The most common ( $\geq 20\%$  on KISQALI plus NSAI and  $\geq 2\%$  higher than placebo) adverse reactions, including laboratory abnormalities, were neutropenia, infections, nausea, headache, fatigue, leukopenia, and abnormal liver function tests.

Table 10 summarizes the adverse reactions in NATALEE.

**Table 10: Adverse Reactions ( $\geq 10\%$  and  $\geq 2\%$  Higher Than NSAI Alone Arm) in NATALEE**

Adverse reaction	KISQALI + NSAI (n = 2526)		NSAI (n = 2441)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Infections and infestations</b>				
Infections <sup>1</sup>	37	2.0	27	0.9
<b>Nervous system disorders</b>				
Headache <sup>2</sup>	23	0.4	17	0.2
<b>Gastrointestinal disorders</b>				
Nausea <sup>2</sup>	23	0.2	8	0.1
Diarrhea <sup>2</sup>	15	0.6	6	0.1
Constipation <sup>2</sup>	13	0.2	5	0
Abdominal pain <sup>2</sup>	11	0.5	7	0.4
<b>General disorders and administration-site conditions</b>				
Fatigue <sup>2</sup>	22	0.8	13	0.2
Asthenia <sup>2</sup>	17	0.6	12	0.1
Pyrexia <sup>2</sup>	11	0.2	6	0.1
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia	15	0	4.6	0
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Cough <sup>2</sup>	13	0.1	8	0.1
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.				
<sup>1</sup> Infections: urinary tract infections; respiratory tract infections.				
<sup>2</sup> Only includes a Grade 3 adverse reaction.				

Clinically relevant adverse reactions reported in  $< 10\%$  of patients who received KISQALI plus NSAI included rash (9%), dizziness (9%), vomiting (8%), peripheral edema (7%), pruritis (7%), dyspnea (7%), stomatitis (6%), oropharyngeal pain (6%), hypocalcemia (5%), hypokalemia (4.8%), decreased appetite (4.8%).

Table 11 summarizes the laboratory abnormalities in NATALEE.

**Table 11: Select Laboratory Abnormalities ( $\geq 10\%$ ) in Patients in NATALEE Who Received KISQALI Plus NSAI**

Laboratory abnormality	KISQALI + NSAI (n = 2526)		NSAI (n = 2441)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Hematology</b>				
Lymphocytes decreased	97	19	88	6
Leukocytes decreased	95	27	45	0.6
Neutrophils decreased	94	45	35	1.7
Hemoglobin decreased	47	0.6	26	0.3
Platelets decreased	28	0.4	13	0.3
<b>Chemistry</b>				
Alanine aminotransferase increased	45	8	35	1
Aspartate aminotransferase increased	44	5	33	1
Creatinine increased	33	0.3	11	0

Adverse reactions listed are based on the data of KISQALI in combination with NSAI [anastrozole or letrozole (FEMARA)]. For the complete list of known adverse reactions with KISQALI or FEMARA, see the Full Prescribing Information of KISQALI or FEMARA.

#### MONALEESA-2: KISQALI in Combination with Letrozole

*Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

The safety of KISQALI was evaluated in MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole [see *Clinical Studies (14)*]. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for  $\geq 12$  months.

Serious adverse reactions occurred in 21% of patients who received KISQALI plus letrozole. Serious adverse reactions in  $\geq 1\%$  of patients receiving KISQALI plus letrozole included abdominal pain (1.5%), vomiting (1.5%), constipation (1.2%), nausea (1.2%), anemia (1.2%), febrile neutropenia (1.2%), dyspnea (1.2%), and alanine aminotransferase increased (1.2%).

Fatal adverse reactions occurred in 1.8% of patients who received KISQALI. Fatal adverse reactions in  $\geq 0.1\%$  of patients receiving KISQALI included acute respiratory failure (0.6%), acute myocardial infarction, sudden death (with Grade 3 hypokalemia and Grade 2 QT prolongation), unknown cause, and pneumonia (0.3% each). Permanent discontinuation of both KISQALI and letrozole due to an adverse reaction occurred in 7% of patients. Permanent discontinuation of KISQALI alone occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and letrozole in  $\geq 2\%$  of patients were alanine aminotransferase increased (5%), aspartate aminotransferase increased (3%), and vomiting (2%).

Dosage interruptions of both KISQALI and letrozole due to an adverse reaction occurred in 71% of patients. Adverse reactions which required dosage interruption in  $\geq 5\%$  of patients included neutropenia (39%), neutrophils decreased (12%), vomiting (6%), nausea (5%), alanine aminotransferase increased (5%), and leukocytes decreased (5%).

Dose reductions due to adverse reaction occurred in 45% of patients receiving KISQALI plus letrozole. Adverse reactions which required dose reductions in  $\geq 2\%$  of patients included neutropenia (24%), neutrophils decreased (8%), and alanine aminotransferase increased (3%).

Antiemetics and antidiarrheal medications were used to manage symptoms as clinically indicated.

The most common ( $\geq 20\%$  on the KISQALI arm and  $\geq 2\%$  higher than placebo) adverse reactions, including laboratory abnormalities, were neutrophils decreased, leukocytes decreased, hemoglobin decreased, nausea, lymphocytes decreased, alanine aminotransferase increased, aspartate aminotransferase increased, fatigue, diarrhea, alopecia, vomiting, platelets decreased, constipation, headache, and back pain.

Table 12 summarizes the adverse reactions in MONALEESA-2.

**Table 12: Adverse Reactions ( $\geq 10\%$  and  $\geq 2\%$  Higher Than Placebo Arm) in MONALEESA-2**

Adverse reaction	KISQALI + Letrozole (n = 334)		Placebo + Letrozole (n = 330)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Gastrointestinal disorders</b>				
Nausea <sup>1</sup>	52	2.4	29	0.6
Diarrhea <sup>1</sup>	35	1.2	22	0.9
Vomiting <sup>1</sup>	29	3.6	16	0.9
Constipation <sup>1</sup>	25	1.2	19	0
Stomatitis <sup>1</sup>	12	0.3	7	0
Abdominal pain <sup>1</sup>	11	1.2	8	0
<b>General disorders and administration-site conditions</b>				
Fatigue	37	2.4	30	0.9
Pyrexia <sup>1</sup>	13	0.3	6	0
Edema peripheral <sup>1</sup>	12	0	10	0
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia <sup>1</sup>	33	0	16	0
Rash <sup>1</sup>	17	0.6	8	0
Pruritus <sup>1</sup>	14	0.6	6	0
<b>Nervous system disorders</b>				
Headache <sup>1</sup>	22	0.3	19	0.3
Insomnia <sup>1</sup>	12	0.3	9	0
<b>Musculoskeletal and connective tissue disorders</b>				

Back pain <sup>1</sup>	20	2.1	18	0.3
<b>Metabolism and nutrition disorders</b>				
Decreased appetite <sup>1</sup>	19	1.5	15	0.3
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dyspnea <sup>1</sup>	12	1.2	9	0.6
<b>Infections and infestations</b>				
Urinary tract infections <sup>1</sup>	11	0.6	8	0
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.				
<sup>1</sup> Only includes Grade 3 adverse reactions.				

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-2 receiving KISQALI plus letrozole included interstitial lung disease (0.3%), lung infiltration (0.3%), pneumonitis (0.3%), and pulmonary fibrosis (0.6%). Table 13 summarizes the laboratory abnormalities in MONALEESA-2.

**Table 13: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-2 Who Received KISQALI Plus Letrozole**

Laboratory abnormality	KISQALI + Letrozole (n = 334)		Placebo + Letrozole (n = 330)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Hematology</b>				
Leukocytes decreased	93	34	29	1.5
Neutrophils decreased	93	60	24	1.2
Hemoglobin decreased	57	1.8	26	1.2
Lymphocytes decreased	51	14	22	3.9
Platelets decreased	29	0.9	6	0.3
<b>Chemistry</b>				
Alanine aminotransferase increased	46	10	36	1.2
Aspartate aminotransferase increased	44	7	32	1.5
Creatinine increased	20	0.6	6	0
Phosphorous decreased	13	5	4	0.6
Potassium decreased	11	1.2	7	1.2

Adverse reactions listed are based on the data of KISQALI in combination with letrozole (FEMARA). For the complete list of known ARs with KISQALI or FEMARA, see the Full Prescribing Information of KISQALI or FEMARA.

#### *Bone Effects*

In MONALEESA-2, with a median duration of safety follow-up of 20.1 months, 12 patients (4%) in the ribociclib plus letrozole arm and 18 patients (6%) in the placebo plus letrozole arm experienced fractures. Osteoporosis (all Grades) was experienced in three patients (0.9%) in the ribociclib plus letrozole arm and 2 patients (0.6%) in the placebo plus letrozole arm.

#### MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor

##### *Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

The safety of KISQALI was evaluated in MONALEESA-7, a clinical trial of 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus NSAI or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin [see *Clinical Studies (14)*]. The median duration of exposure in the KISQALI plus a NSAI arm was 15.2 months with 66% of patients exposed for ≥ 12 months. The safety data reported below are based on 495 pre/perimenopausal patients receiving KISQALI plus NSAI plus goserelin or placebo plus NSAI plus goserelin.

Serious adverse reactions occurred in 17% of patients who received KISQALI plus NSAI plus goserelin. Serious adverse reactions in ≥ 1% of patients receiving KISQALI plus NSAI plus goserelin included drug-induced liver injury (1.6%), abdominal pain (1.2%), dyspnea (1.2%), febrile neutropenia (1.2%), and back pain (1.2%).

Permanent discontinuation of both KISQALI and NSAI due to an adverse reaction occurred in 3% of patients. Permanent discontinuation of KISQALI alone occurred in 3% patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and NSAI in  $\geq 2\%$  of patients were alanine aminotransferase increased (2%), and aspartate aminotransferase increased (2%).

Dosage interruptions of KISQALI plus NSAI plus goserelin due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in  $\geq 5\%$  of patients included neutropenia (41%), neutrophils decreased (26%), and leukocytes decreased (6%).

Dose reductions due to an adverse reaction occurred in 33% of patients receiving KISQALI plus NSAI plus goserelin. Adverse reactions which required dose reductions in  $\geq 2\%$  of patients included neutropenia (17%), neutrophils decreased (5%), and alanine aminotransferase increased (2%).

The most common ( $\geq 20\%$  on the KISQALI arm and  $\geq 2\%$  higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, infections, arthralgia, alanine aminotransferase increased, nausea, platelets decreased, and alopecia.

Table 14 summarizes the adverse reactions in MONALEESA-7.

**Table 14: Adverse Reactions ( $\geq 10\%$  and  $\geq 2\%$  Higher Than Placebo Arm) in MONALEESA-7 (NSAI)**

Adverse reaction	KISQALI + NSAI + Goserelin (n = 248)		Placebo + NSAI + Goserelin (n = 247)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Infections and infestations</b>				
Infections <sup>1,2</sup>	36	1.6	24	0.4
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia <sup>2</sup>	34	0.8	29	1.2
<b>Gastrointestinal disorders</b>				
Nausea <sup>2</sup>	32	0	20	0
Constipation <sup>2</sup>	16	0	12	0
Stomatitis <sup>2</sup>	10	0	8	0.4
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia <sup>2</sup>	21	0	13	0
Rash <sup>2</sup>	17	0.4	9	0
Pruritus <sup>2</sup>	11	0	4	0
<b>General disorders and administration-site conditions</b>				
Pyrexia <sup>2</sup>	17	0.8	7	0
Pain in extremity <sup>2</sup>	10	0	8	1.2
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough <sup>2</sup>	15	0	10	0
Abbreviation: NSAI, non-steroidal aromatase inhibitor. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. <sup>1</sup> Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%). <sup>2</sup> Only includes Grade 3 adverse reactions.				

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-7 receiving KISQALI plus NSAI included thrombocytopenia (9%), dry skin (9%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia (2%), blood bilirubin increased (1%), syncope (0.4%), and pneumonitis (0.4%).

**Table 15: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-7 Who Received KISQALI Plus NSAI Plus Goserelin**

Laboratory abnormality	KISQALI + NSAI + Goserelin (n = 248)		Placebo + NSAI + Goserelin (n = 247)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
<b>Hematology</b>				
Leukocytes decreased	93	36	30	0.8
Neutrophils decreased	92	63	27	2.4
Hemoglobin decreased	84	2.4	51	0.4
Lymphocytes decreased	55	14	18	2.8
Platelets decreased	26	0.4	9	0.4
<b>Chemistry</b>				
Gamma-glutamyl transferase increased	42	7	42	9
Aspartate aminotransferase increased	37	4.8	35	1.6
Alanine aminotransferase increased	33	6	31	1.6
Phosphorous decreased	14	1.6	11	0.8
Potassium decreased	11	1.2	14	1.2
Glucose serum decreased	10	0.4	10	0.4
Creatinine increased	8	0	2	0

Adverse reactions listed are based on the data of KISQALI in combination with NSAI [anastrozole or letrozole (FEMARA)]. For the complete list of known adverse reactions with KISQALI or FEMARA, see the Full Prescribing Information of KISQALI or FEMARA.

#### *Bone Effects*

In MONALEESA-7, with a median duration of safety follow-up of 26.5 months, 4 patients (2%) in the ribociclib plus NSAI subgroup and 7 patients (3%) in the placebo plus NSAI subgroup experienced fractures. No osteoporosis (all Grades) was reported in the ribociclib plus NSAI subgroup, and 1 patient (0.4%) experienced osteoporosis in the placebo plus NSAI subgroup.

#### COMPLEMENT-1: KISQALI in Combination with Letrozole and Goserelin or Leuprolide

##### *Men with HR-positive, HER2-negative Advanced Breast Cancer for Initial Endocrine-Based Therapy*

The safety of KISQALI in combination with letrozole was evaluated in men (n = 39) in an open-label, multicenter clinical study for the treatment of adult patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEMENT-1) [see *Clinical Studies (14)*].

The median duration of exposure to KISQALI was 20.8 months (range, 0.5 to 30.6 months).

Other adverse reactions occurring in men treated with KISQALI plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with KISQALI plus endocrine therapy.

## **6.2 Postmarketing Experience**

The following adverse events have been reported during post-approval use of KISQALI. Because these events 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/pneumonitis

*Skin and subcutaneous tissue disorders:* Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia, and systemic symptoms (DRESS).



## 7 DRUG INTERACTIONS

### Ribociclib

#### 7.1 Drugs That May Increase Ribociclib Plasma Concentrations

##### CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitors increases ribociclib exposure [see *Clinical Pharmacology* (12.3)]. Increased ribociclib concentrations may increase the incidence and severity of adverse reactions, including QTcF prolongation [see *Warnings and Precautions* (5.3)]. Avoid concomitant use of strong CYP3A inhibitors with KISQALI and consider alternative concomitant medications with less potential for CYP3A inhibition.

In patients with early breast cancer, if coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 200 mg once daily. In patients with advanced or metastatic breast cancer, if coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily [see *Dosage and Administration* (2.2)].

#### 7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

##### CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducers decreases the plasma exposure of ribociclib [see *Clinical Pharmacology* (12.3)]. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A.

#### 7.3 Effect of KISQALI on Other Drugs

##### CYP3A Substrates

Coadministration of sensitive CYP3A4 substrates with multiple doses of KISQALI increases the substrate exposure [see *Clinical Pharmacology* (12.3)]. For CYP3A substrates where minimal increases in the concentration may increase CYP3A substrate adverse reactions, monitor for increased adverse reactions of the CYP3A substrate during treatment with KISQALI. The dose of a sensitive CYP3A substrate may need to be reduced as KISQALI can increase its exposure.

#### 7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with products with a known potential to prolong QT interval, such as antiarrhythmic drugs that are known to prolong the QT interval. If concomitant use cannot be avoided, monitor ECG when initiating, during concomitant use, and as clinically indicated [see *Warnings and Precautions* (5.3), *Clinical Pharmacology* (12.2)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings from animal studies and the mechanisms of action, KISQALI FEMARA CO-PACK 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. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of post implantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC (see *Data*). Advise pregnant women of the potential risk to a fetus.

In animal reproduction studies, administration of letrozole to pregnant animals during organogenesis resulted in increased post-implantation pregnancy loss and resorptions, fewer live fetuses, and fetal malformations affecting the renal and skeletal systems in rats and rabbits at doses approximately 0.1 times the daily MRHD on a mg/m<sup>2</sup> basis (see *Data*).

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

## Data

### *Animal Data - Ribociclib*

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses  $\geq 30$  mg/kg/day, there were adverse effects on embryo-fetal development, including increased incidences of fetal abnormalities (malformations and external, visceral, and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13<sup>th</sup> ribs, misshapen hyoid bone, bent hyoid bone alae and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

### *Animal Data - Letrozole*

In a fertility and early embryonic developmental toxicity study in female rats, oral administration of letrozole starting 2 weeks before mating until pregnancy day 6 resulted in an increase in pre-implantation loss at doses  $\geq 0.003$  mg/kg/day (approximately 0.01 times the MRHD on a mg/m<sup>2</sup> basis).

In an embryo-fetal developmental toxicity study in rats, daily administration of oral letrozole during the period of organogenesis at doses  $\geq 0.003$  mg/kg (approximately 0.01 times the MRHD on a mg/m<sup>2</sup> basis) resulted in embryo-fetal toxicity, including intrauterine mortality, increased resorptions and postimplantation loss, decreased numbers of live fetuses and fetal anomalies, including absence and shortening of renal papilla, dilation of ureter, edema and incomplete ossification of frontal skull and metatarsals. Letrozole was teratogenic to rats at a dose of 0.03 mg/kg (approximately 0.1 times the MRHD on a mg/m<sup>2</sup> basis) and caused fetal domed head and cervical/centrum vertebral fusion.

In an embryo-fetal developmental toxicity study in rabbits, daily administration of oral letrozole during the period of organogenesis at doses  $\geq 0.002$  mg/kg (approximately 0.01 the MRHD on a mg/m<sup>2</sup> basis) resulted in embryo-fetal toxicity, including increased resorptions, increased postimplantation loss and decreased numbers of live fetuses. Fetal anomalies included incomplete ossification of the skull, sternebrae, and fore- and hind legs.

## **8.2 Lactation**

### Risk Summary

It is not known if ribociclib and letrozole are present in human milk. There are no data on the effects of ribociclib and/or letrozole on the breastfed infant or milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats (*see Data*). Exposure of lactating rats to letrozole was associated with an impaired reproductive performance of the male offspring (*see Data*). Because of the potential for serious adverse reactions in breastfed infants from KISQALI FEMARA CO-PACK, advise lactating women not to breastfeed while taking KISQALI FEMARA CO-PACK and for at least 3 weeks after the last dose.

## Data

### *Animal Data - Ribociclib*

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

### *Animal Data - Letrozole*

In a postnatal developmental toxicity study in lactating rats, letrozole was administered orally at doses of 1, 0.003, 0.03 or 0.3 mg/kg/day on Day 0 through Day 20 of lactation. The reproductive performance of the male offspring was impaired at a letrozole dose as low as 0.003 mg/kg/day (approximately 0.01 the MRHD on a mg/m<sup>2</sup> basis), as reflected by decreased mating and pregnancy ratios. There were no effects on the reproductive performance of female offspring.

### 8.3 Females and Males of Reproductive Potential

Based on animal studies and mechanisms of action, KISQALI FEMARA CO-PACK 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 starting treatment with KISQALI FEMARA CO-PACK.

#### Contraception

##### *Females*

Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI FEMARA CO-PACK and for at least 3 weeks after the last dose.

#### Infertility

##### *Females*

Based on studies with letrozole in female animals, KISQALI FEMARA CO-PACK may impair fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1)*].

##### *Males*

Based on animal studies in males, KISQALI FEMARA CO-PACK may impair fertility in males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

### 8.4 Pediatric Use

The safety and efficacy of KISQALI FEMARA CO-PACK in pediatric patients have not been established.

Letrozole administration to young (postnatal Day 7) rats for 12 weeks duration at 0.003, 0.03, 0.3 mg/kg/day by oral gavage resulted in adverse skeletal/growth effects (bone maturation, bone mineral density) and neuroendocrine and reproductive developmental perturbations of the hypothalamic-pituitary axis. Administration of 0.3 mg/kg/day resulted in AUC values that were similar to the AUC in adult patients receiving the recommended dose of 2.5 mg/day. Decreased fertility was accompanied by hypertrophy of the hypophysis and testicular changes that included degeneration of the seminiferous tubular epithelium and atrophy of the female reproductive tract. Young rats in this study were allowed to recover following discontinuation of letrozole treatment for 42 days. Histopathological changes were not reversible at clinically relevant exposures.

### 8.5 Geriatric Use

Of the 2549 adults with early breast cancer who received KISQALI in NATALEE, 407 patients (16%) were  $\geq 65$  years of age and 123 patients (2.4%) were  $\geq 75$  years of age. No overall differences in safety or effectiveness of KISQALI were observed between older and younger adults with early breast cancer.

Of 334 patients with advanced or metastatic breast cancer who received KISQALI plus letrozole in MONALEESA-2, 150 patients (45%) were  $\geq 65$  years of age and 35 patients (11%) were  $\geq 75$  years of age. No overall differences in safety or effectiveness of KISQALI plus letrozole were observed between older and younger adults with advanced or metastatic breast cancer. Of 248 patients with advanced or metastatic breast cancer who received KISQALI in MONALEESA-7, no patients were  $\geq 65$  years of age.

### 8.6 Hepatic Impairment

No dose adjustment of KISQALI is necessary in patients with breast cancer who have mild hepatic impairment (Child-Pugh class A) [*see Clinical Pharmacology (12.3)*]. A reduced starting dose of 400 mg KISQALI is recommended in patients with advanced or metastatic breast cancer who have moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) [*see Dosage and Administration (2.2)*].

No dose adjustment of FEMARA is necessary in patients with breast cancer who have mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment. The dose of FEMARA in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50% [*see Clinical Pharmacology (12.3)*]. The recommended dose of FEMARA for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on FEMARA exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined [*see Clinical Pharmacology (12.3)*].

## 8.7 Renal Impairment

No dose adjustment of KISQALI is necessary in patients breast cancer who have mild to moderate (30 mL/min to 89 mL/min/ $1.73\text{ m}^2 \leq$  estimated glomerular filtration rate (eGFR)) renal impairment. A reduced starting dose of 200 mg of KISQALI is recommended in patients with breast cancer who have severe renal impairment [see *Dosage and Administration* (2.2), *Clinical Pharmacology* (12.3)].

No dosage adjustment of FEMARA is required for patients with renal impairment if creatinine clearance is greater than or equal to 10 mL/min [see *Dosage and Administration* (2.2), *Clinical Pharmacology* (12.3)].

## 11 DESCRIPTION

KISQALI FEMARA CO-PACK consists of ribociclib 200 mg film-coated tablets co-packaged with letrozole 2.5 mg tablets.

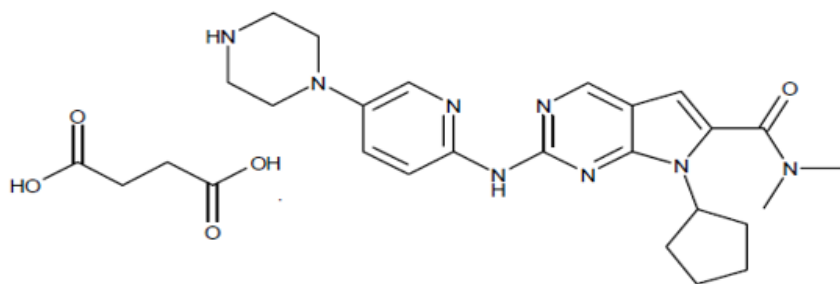
### Ribociclib

KISQALI (ribociclib) is a kinase inhibitor.

Ribociclib succinate is a light yellow to yellowish brown crystalline powder. The chemical name of ribociclib succinate is: Butanedioic acid—7-cyclopentyl-*N,N*-dimethyl-2- {[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1).

The molecular formula for ribociclib succinate is  $\text{C}_{23}\text{H}_{30}\text{N}_8\text{O} \cdot \text{C}_4\text{H}_6\text{O}_4$  and the molecular weight is 552.64 g/mol [*Free base*: 434.55 g/mol].

The chemical structure of ribociclib is shown below:



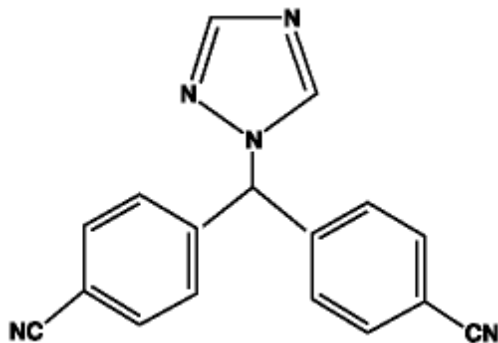
KISQALI film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate, and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

### Letrozole

FEMARA (letrozole) is a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis).

Letrozole is a white to yellowish crystalline powder, practically odorless, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. It has a molecular weight of 285.31 g/mol, empirical formula  $\text{C}_{17}\text{H}_{11}\text{N}_5$ , and a melting range of 184°C to 185°C.

The chemical name of letrozole is 4,4'-(1*H*-1,2,4-Triazol-1-ylmethylene) dibenzonitrile, and its structural formula is



FEMARA is available as 2.5 mg tablets for oral administration.

Inactive Ingredients: colloidal silicon dioxide, ferric oxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and are downstream of signaling pathways, which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

*In vitro*, ribociclib decreased pRb phosphorylation, resulting in arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer-derived lines. *In vivo*, treatment with single agent ribociclib in a rat xenograft model with human tumor cells led to decreased tumor volumes, which correlated with inhibition of pRb phosphorylation.

Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

In studies, using patient-derived estrogen receptor positive breast cancer xenograft models, combination of ribociclib and antiestrogen (e.g., letrozole) therapies resulted in increased tumor growth inhibition compared to each drug alone.

### 12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of KISQALI have not been fully characterized in patients.

#### Ribociclib

##### Cardiac Electrophysiology

A concentration-QT analysis of the data in patients with breast cancer treated with KISQALI at doses ranging from 50 to 1200 mg (0.083 to 2 times of the approved recommended high dose) suggested that ribociclib causes concentration-dependent increases in the QTcF interval.

In patients with early breast cancer, the estimated mean QTcF interval change from baseline for the KISQALI 400 mg in combination with non-steroidal aromatase inhibitor (NSAI) was 10.0 ms (90% CI: 8.0, 11.9) at the mean steady-state  $C_{max}$  [see *Warnings and Precautions* (5.3, 5.4)].

In patients with advanced or metastatic breast cancer the estimated mean QTcF interval change from baseline for KISQALI 600 mg in combination with aromatase inhibitors was 22.0 ms (90% CI: 22.0, 23.4), and was 34.7 ms (90% CI: 31.6, 37.8) in combination with tamoxifen at the mean  $C_{max}$  at steady-state [see *Warnings and Precautions* (5.3)].

#### Letrozole

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg FEMARA (letrozole) suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75% to 95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate that were below the limit of detection in the assays. Estrogen suppression was maintained throughout treatment in all patients treated at 0.5 mg or higher.

Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of adrenal steroidogenesis. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, adrenocorticotrophic hormone (ACTH) or in plasma renin activity among postmenopausal patients treated with a daily dose of FEMARA 0.1 mg to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Glucocorticoid or mineralocorticoid supplementation is, therefore, not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses of FEMARA or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg. This indicates that the blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were not affected by letrozole in patients, nor was thyroid function as evaluated by thyroid stimulating hormone (TSH) levels, T3 uptake, and T4 levels.

### 12.3 Pharmacokinetics

Ribociclib exhibited over-proportional increases in exposure ( $C_{max}$  and AUC) across the dose range of 50 mg to 1200 mg (0.083 to 2 times of the approved recommended high dose) following both single dose and repeated doses of KISQALI. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and ribociclib accumulated with a mean accumulation ratio of 2.5 (range, 0.97 to 6.4) and mean (coefficient of variation (CV%)) steady-state ribociclib  $C_{max}$  was 1820 (62%) ng/mL and AUC was 23800 (66%) ng\*h/mL.

Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur.

#### Absorption

##### **Ribociclib**

The  $T_{max}$  following KISQALI administration was between 1 and 4 hours. The mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8%.

*Food Effect:* Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI tablet with a high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) had no clinically meaningful differences in ribociclib  $C_{max}$  or  $AUC_{inf}$ .

##### **Letrozole**

Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine.

Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg).

#### Metabolism and Elimination/Excretion

##### **Ribociclib**

Ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of radio-labeled ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure. Clinical activity of ribociclib was due primarily to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. Metabolite LEQ803 represented approximately 14% and 4% of the administered dose in feces and urine, respectively.

#### Elimination

The mean plasma effective half-life (CV%) was 32.0 hours (63%) and the mean apparent oral clearance (CL/F) was 25.5 L/hr (66%) at steady-state following 600 mg dose of KISQALI in patients with advanced cancer. The steady state mean CL/F was 38.4 L/hr following the 400 mg dose of KISQALI in patients with early breast cancer.

The mean apparent plasma terminal half-life of ribociclib ranged from 29.7 to 54.7 hours and mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy adults.

Following a single oral dose of radio-labeled ribociclib in healthy adults, 92% of the total administered radioactive dose was recovered within 22 days; 69% in feces and 23% in urine.

## **Letrozole**

Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75% was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged letrozole.

In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, letrozole inhibited CYP2A6 and inhibited CYP2C19, however, the clinical significance of these findings is unknown.

### Specific Populations

#### *Patients with Hepatic Impairment*

## **Ribociclib**

Compared to adults with normal hepatic impairment, mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of ribociclib; while in adults with moderate (Child-Pugh class B) hepatic impairment, the mean ratio was 1.44 for  $C_{\max}$  and 1.28 for  $AUC_{\inf}$ ; and with adults with severe (Child-Pugh class C) hepatic impairment, the mean ratio was 1.32 for  $C_{\max}$  and 1.29 for  $AUC_{\inf}$ .

## **Letrozole**

The effect of hepatic impairment on FEMARA exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

In a study of subjects with mild to moderate non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh class A and B), the mean AUC values of the volunteers with moderate hepatic impairment were 37% higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a pharmacokinetic study, subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh class C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had 2-fold increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients with normal liver function receiving similar doses of this drug [see *Clinical Pharmacology* (12.3)].

#### *Patients with Renal Impairment*

## **Ribociclib**

In adults with severe renal impairment and end stage renal disease, ribociclib  $AUC_{\inf}$  increased 2.4-fold and 3.8-fold, and  $C_{\max}$  increased 2.1-fold and 2.7-fold relative to the exposure in adults with normal renal function.

Mild or moderate renal impairment had no effect on the exposure of ribociclib. In a subgroup analysis of data from studies following oral administration of KISQALI in patients with advanced cancer or early breast cancer who have mild to moderate renal impairment, AUC and  $C_{\max}$  were comparable to those in patients with normal renal function, suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure.

## **Letrozole**

In a study of volunteers with varying renal function (24-hour creatinine clearance: 9 to 116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg of FEMARA was found. In addition, in a study of 347 patients with advanced breast cancer, about half of whom received 2.5 mg FEMARA and half 0.5 mg FEMARA, renal impairment (calculated creatinine clearance: 20 to 50 mL/min) did not affect steady-state plasma letrozole concentrations.

#### *Effect of Age, Weight, Gender, and Race*

No clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib were identified.

## Drug Interaction Studies

### Clinical Studies and Model-Informed Approaches

#### *Drugs That Affect Ribociclib Plasma Concentrations*

**CYP3A Inhibitors:** Following a single 400 mg dose of KISQALI with ritonavir (a strong CYP3A inhibitor), ritonavir (100 mg twice a day for 14 days) increased ribociclib  $C_{\max}$  and  $AUC_{\inf}$  by 1.7-fold and 3.2-fold, respectively, compared to ribociclib alone.  $C_{\max}$  and AUC for LEQ803 (a prominent metabolite of LEE011, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. A moderate CYP3A4 inhibitor (erythromycin) is predicted to increase ribociclib steady-state  $C_{\max}$  and AUC by 1.1-fold and 1.2-fold, respectively, following KISQALI 400 mg once daily, and 1.1-fold and 1.1-fold respectively, following KISQALI 600 mg once daily.

**CYP3A Inducers:** Following a single 600 mg dose of KISQALI with rifampicin (a strong CYP3A4 inducer) at 600 mg daily for 14 days, ribociclib  $C_{\max}$  decreased by 81% and  $AUC_{\inf}$  decreased by 89%, while LEQ803  $C_{\max}$  increased 1.7-fold and  $AUC_{\inf}$  decreased by 27% compared to ribociclib alone. A moderate CYP3A inducer (efavirenz) is predicted to decrease ribociclib steady-state  $C_{\max}$  by 55% and AUC by 74%, following KISQALI 400 mg once daily, and by 52% and 71% respectively, following KISQALI 600 mg once daily.

#### *Drugs That Are Affected by KISQALI*

**CYP3A4 and CYP1A2 Substrates:** In a cocktail study with midazolam (sensitive CYP3A4 substrate) multiple doses of ribociclib (400 mg once daily for 8 days) increased midazolam  $C_{\max}$  by 2.1-fold and increased  $AUC_{\inf}$  by 3.8-fold compared to midazolam alone. Administration of KISQALI 600 mg once daily is predicted to increase midazolam  $C_{\max}$  and AUC by 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of 400 mg ribociclib on caffeine (sensitive CYP1A2 substrate) was minimal, with  $C_{\max}$  decreased by 10% and  $AUC_{\inf}$  increased slightly by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted at KISQALI 600 mg once daily dose.

**Gastric pH-Elevating Agents:** Coadministration of ribociclib with drugs that elevate the gastric pH is not predicted to alter ribociclib absorption.

**Letrozole:** Data from a clinical trial in patients with breast cancer indicated no drug interaction between ribociclib and letrozole following coadministration of the drugs.

**Anastrozole:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following coadministration of the drugs.

**Exemestane:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following coadministration of the drugs.

**Fulvestrant:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant effect of fulvestrant on ribociclib exposure following coadministration of the drugs.

**Tamoxifen:** KISQALI is not indicated for concomitant use with tamoxifen. Data from a clinical trial in patients with breast cancer indicated that tamoxifen  $C_{\max}$  and AUC increased approximately 2-fold following coadministration of KISQALI 600 mg.

#### *In Vitro Studies*

**Effect of Ribociclib on CYP Enzymes:** *In vitro*, ribociclib was a reversible inhibitor of CYP1A2, CYP2E1, and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. *In vitro* evaluations indicated that ribociclib has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. It has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6, and no induction of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 at clinically relevant concentrations.

**Effect of Ribociclib on Transporters:** *In vitro* evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations.

**Effect of Transporters on Ribociclib:** Based on *in vitro* data, P-gp, and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro*.



## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Ribociclib

In a 2-year carcinogenicity study with oral administration of ribociclib daily in cycles of 3 weeks on/1 week off, ribociclib was not carcinogenic at doses up to 50 mg/kg in male rats and 600 mg/kg in female rats. Systemic exposure in male and female rats were 1.3 and 1.8 times, respectively, the human exposure at the highest recommended dose of 600 mg/day based on AUC.

Ribociclib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay.

In a fertility and early embryonic development study, female rats received oral doses of ribociclib for 14 days prior to mating through the first week of pregnancy. Ribociclib did not affect reproductive function, fertility or early embryonic development at doses up to 300 mg/kg/day (approximately 0.6 times the clinical exposure in patients at the highest recommended dose of 600 mg/day based on AUC).

A fertility study in male rats has not been performed with ribociclib. In repeat-dose toxicity studies with oral administration of ribociclib daily for 3 weeks on/1 week off in rats up to 26 weeks duration and dogs up to 39 weeks duration, atrophic changes in testes were reported. Findings included degeneration of seminiferous tubular epithelia in the testes and hypospermia and luminal cellular debris in the epididymides of rats and dogs and vacuolation of epithelia in the epididymides of rats. These findings were observed at doses  $\geq 75$  mg/kg in rats and  $\geq 1$  mg/kg in dogs which resulted in systemic exposures that were 1.4 and 0.03 times the human exposure at the highest recommended daily dose of 600 mg/day based on AUC, respectively. These effects can be linked to a direct anti-proliferative effect on the testicular germ cells resulting in atrophy of the seminiferous tubules and showed a trend towards reversibility in rats and dogs after a four-week, non-dosing period.

#### Letrozole

A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about 1 to 100 times the daily MRHD on a mg/m<sup>2</sup> basis) administered by oral gavage for up to 2 years revealed a dose-related increase in the incidence of benign ovarian stromal tumors. The incidence of combined hepatocellular adenoma and carcinoma showed a significant trend in females when the high dose group was excluded due to low survival. In a separate study, plasma AUC<sub>0-12hr</sub> levels in mice at 60 mg/kg/day were 55 times higher than the AUC<sub>0-24hr</sub> level in breast cancer patients at the recommended dose. The carcinogenicity study in rats at oral doses of 0.1 to 10 mg/kg/day (about 0.4 to 40 times the daily MRHD on a mg/m<sup>2</sup> basis) for up to 2 years also produced an increase in the incidence of benign ovarian stromal tumors at 10 mg/kg/day. Ovarian hyperplasia was observed in females at doses equal to or greater than 0.1 mg/kg/day. At 10 mg/kg/day, plasma AUC<sub>0-24hr</sub> levels in rats were 80 times higher than the level in breast cancer patients at the recommended dose. The benign ovarian stromal tumors observed in mice and rats were considered to be related to the pharmacological inhibition of estrogen synthesis and may be due to increased luteinizing hormone resulting from the decrease in circulating estrogen.

Letrozole was not mutagenic in *in vitro* tests (Ames and *E.coli* bacterial tests) but was observed to be a potential clastogen in *in vitro* assays [Chinese hamster ovary (CHO) K1 and CCL61 CHO cells]. Letrozole was not clastogenic *in vivo* (micronucleus test in rats).

In a fertility and early embryonic developmental toxicity study in female rats, oral administration of letrozole starting 2 weeks before mating until pregnancy Day 6 resulted in decreases in the incidence of successful mating and pregnancy at doses  $\geq 0.03$  mg/kg/day (approximately 0.1 times the recommended human dose on a mg/m<sup>2</sup> basis). In repeat-dose toxicity studies, administration of letrozole caused sexual inactivity in females and atrophy of the reproductive tract in males and females at doses of 0.6, 0.1, and 0.03 mg/kg in mice, rats and dogs, respectively (approximately 1, 0.4, and 0.4 times the daily MRHD on a mg/m<sup>2</sup> basis, respectively).

## 13.2 Animal Toxicology and/or Pharmacology

### Ribociclib

*In vivo* cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at an exposure similar to patients receiving the recommended dose of 600 mg. There is a potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 5-fold the anticipated clinical  $C_{max}$ ).

## 14 CLINICAL STUDIES

### 14.1 Early Breast Cancer

#### NATALEE: KISQALI in Combination with a Non-steroidal Aromatase Inhibitor (NSAI) with or without Goserelin

##### *Adults with HR-positive, HER2-negative Stage II and III Early Breast Cancer at High Risk of Recurrence*

NATALEE (NCT03701334) was a randomized (1:1), open-label, multicenter study in adults (N = 5101) with HR-positive, HER2-negative early breast cancer that was:

- Anatomic Stage Group IIB-III, or
- Anatomic Stage Group IIA that is either:
  - Node positive or
  - Node negative, with:
    - Histologic Grade 3, or
    - Histologic Grade 2, with any of the following criteria:
      - $Ki67 \geq 20\%$
      - High risk by gene signature testing

Applying TNM criteria, NATALEE included patients with any lymph node involvement, or if no nodal involvement either tumor size > 5 cm, or tumor size 2 to 5 cm with either Grade 2 (and high genomic risk or  $Ki67 \geq 20\%$ ) or Grade 3.

Participants were randomized to receive KISQALI 400 mg plus a non-steroidal aromatase inhibitor (NSAI, letrozole or anastrozole) or NSAI only, and goserelin as indicated. Randomization was stratified by Anatomic Stage, prior treatment (neoadjuvant versus adjuvant chemotherapy), menopausal status (premenopausal and males versus postmenopausal) and region (North America/Western Europe/Oceania versus rest of the world).

The main efficacy outcome measure was invasive disease-free survival (iDFS). iDFS was defined as the time from randomization to the first occurrence of: local invasive breast recurrence, regional invasive recurrence, distant recurrence, death (any cause), contralateral invasive breast cancer, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin). Overall survival (OS) was an additional outcome measure.

KISQALI was given orally at a dose of 400 mg once daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg or anastrozole 1 mg orally once daily for 28 days; goserelin 3.6 mg was administered on Day 1 of each 28-day cycle. KISQALI was administered for up to 36 months in the absence of recurrence or unacceptable toxicity. NSAI was administered for at least 5 years.

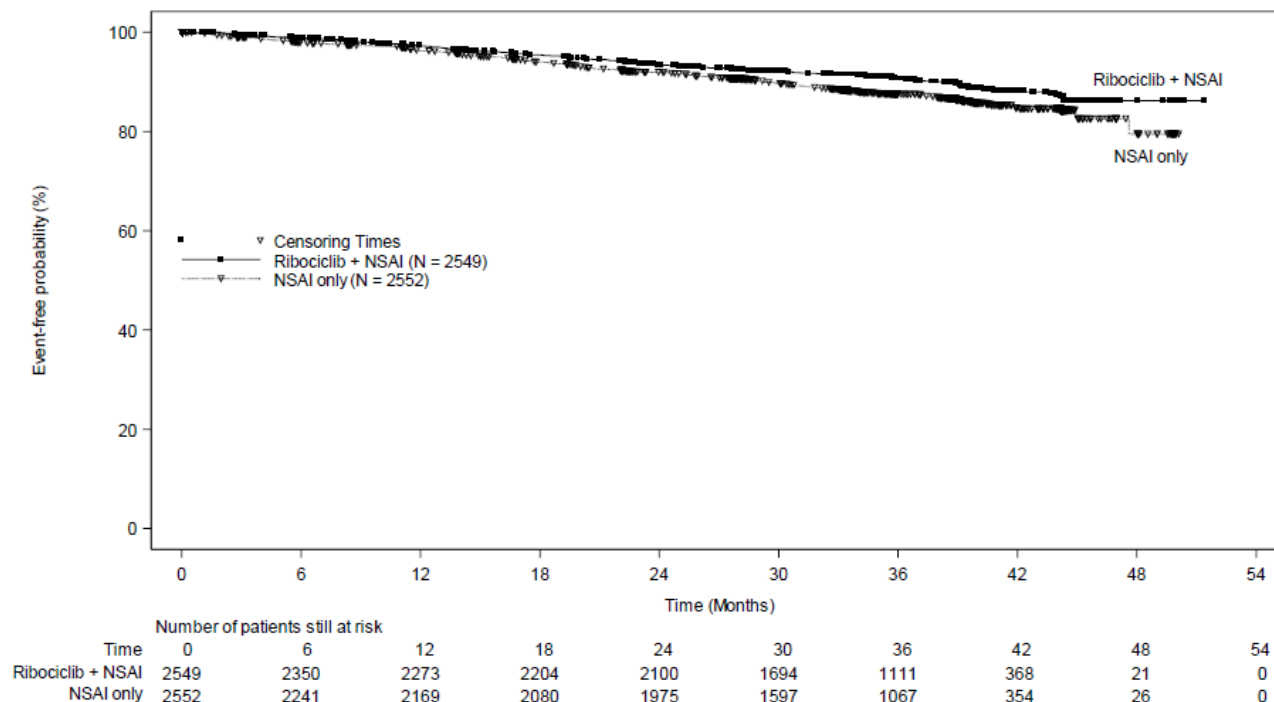
The median age was 52 years (range, 24 to 90); > 99% women (n = 19 men); 73% White, 13% Asian, 1.7% Black or African American, < 0.1% Native Hawaiian or other Pacific Islander, < 0.1% American Indian or Alaskan Native; 8.5% Hispanic or Latino; 99% ECOG 0-1; 88% node positive disease; 88% received prior (neo)adjuvant chemotherapy.

A statistically significant improvement in iDFS was observed in the intent-to-treat (ITT) population at an interim analysis. The efficacy results at the time of the final iDFS analysis are summarized in Table 16 and Figure 1. At the time of the iDFS final analysis, OS was immature, and a total of 172 (3.5%) of patients had died across both study arms.

**Table 16: Efficacy Results – NATALEE (Investigator Assessment, Intent-to-Treat Population)**

	KISQALI + NSAI +/- Goserelin	NSAI +/- Goserelin
<b>Invasive Disease-Free Survival (iDFS)<sup>a</sup></b>	<b>N = 2549</b>	<b>N = 2552</b>
Events (n, %)	226 (8.9%)	283 (11.1%)
Hazard ratio (95% CI)	0.749 (0.628 to 0.892)	
iDFS at 36 months (%; 95% CI)	90.7 (89.3, 91.8)	87.6 (86.1, 88.9)

Abbreviations: CI, confidence interval; iDFS, invasive disease-free survival.  
<sup>a</sup> iDFS was statistically significant at an interim analysis based on a one-sided stratified log-rank p-value of 0.0014.

**Figure 1: Kaplan-Meier Plot of iDFS – NATALEE (Investigator Assessment, Intent-to-Treat Population)**

## 14.2 Advanced or Metastatic Breast Cancer

### MONALEESA-2: KISQALI in Combination with Letrozole

*Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

MONALEESA-2 (NCT01958021) was a randomized (1:1), double-blind, placebo-controlled, multicenter clinical study of KISQALI plus letrozole vs. placebo plus letrozole conducted in postmenopausal women (N = 668) with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.

Participants were randomized to receive either KISQALI and letrozole or placebo and letrozole, stratified according to the presence of liver and/or lung metastases. Letrozole 2.5 mg was given orally once daily for 28 days, with either KISQALI 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

The median age of 62 years (range, 23 to 91) and 45% of patients were older than 65. The majority of patients were White (82%), and all patients had an ECOG performance status of 0 or 1. A total of 47% of patients had received chemotherapy and 51% had received anti-hormonal therapy in the neoadjuvant or adjuvant setting. Thirty-four percent (34%) of patients had de novo metastatic disease, 21% had bone-only disease, and 59% had visceral disease.

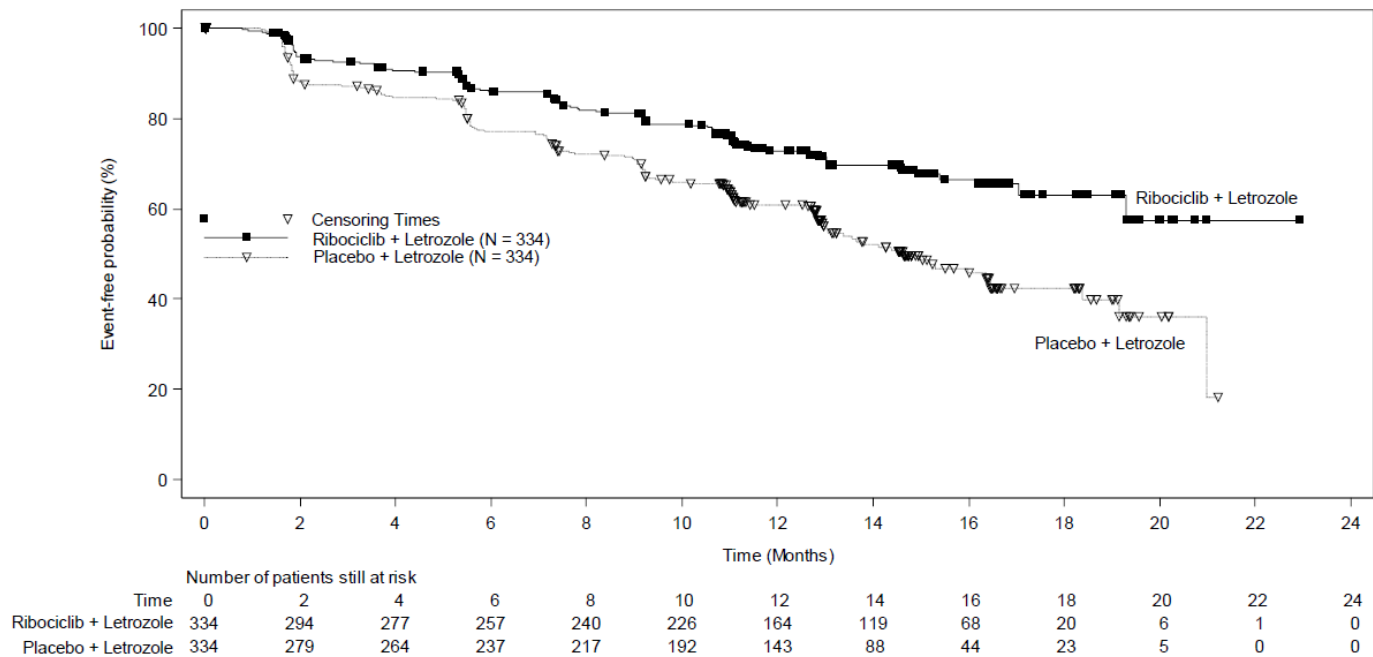
The efficacy results are summarized in Table 17, Figure 2, and Figure 3. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment.

Consistent results were observed across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease.

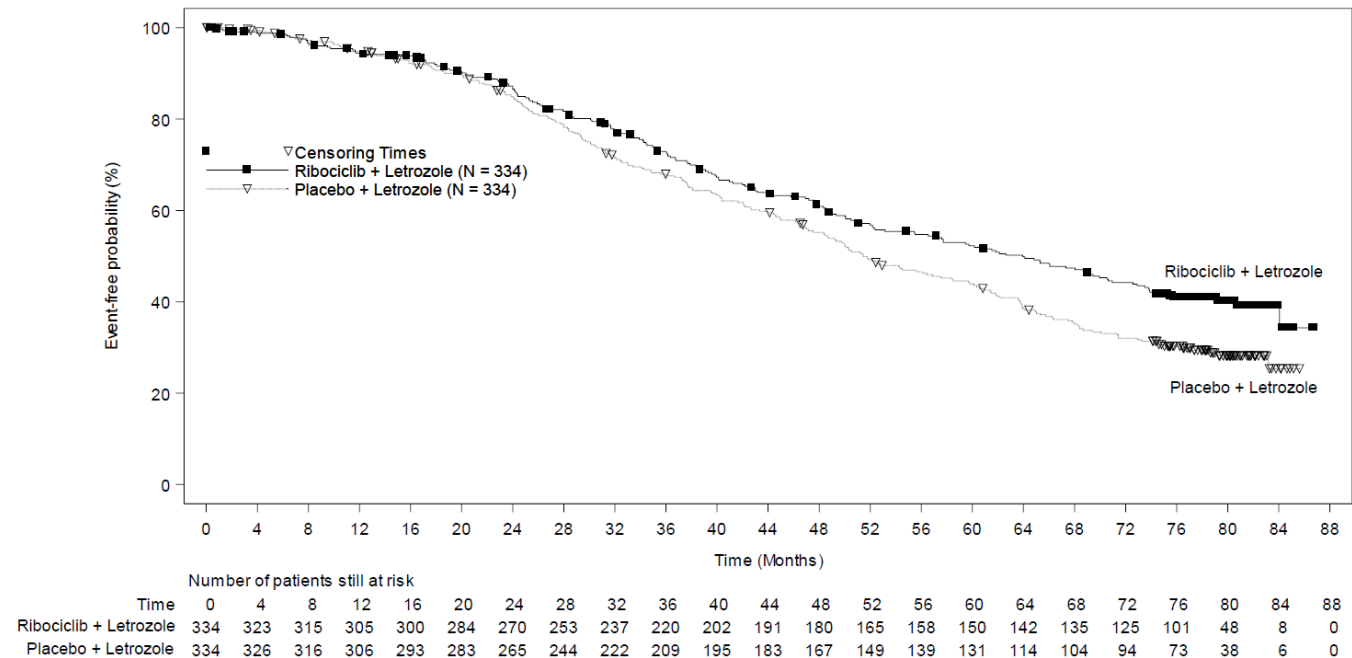
**Table 17: Efficacy Results – MONALEESA-2 (Investigator Assessment, Intent-to-Treat Population)**

	<b>KISQALI + Letrozole</b>	<b>Placebo + Letrozole</b>
<b>Progression-Free Survival</b>	<b>N = 334</b>	<b>N = 334</b>
Events (n, %)	93 (27.8)	150 (44.9)
Median (months, 95% CI)	NR (19.3 – NR)	14.7 (13.0 – 16.5)
Hazard ratio (95% CI)	0.556 (0.429, 0.720)	
p-value <sup>a</sup>	< 0.0001 <sup>a</sup>	
<b>Overall Survival</b>	<b>N = 334</b>	<b>N = 334</b>
Events (n, %)	181 (54.2)	219 (65.6)
Median (months, 95% CI)	63.9 (52.4, 71.0)	51.4 (47.2, 59.7)
Hazard ratio (95% CI)	0.765 (0.628, 0.932)	
p-value	0.004 <sup>a</sup>	
<b>Overall Response Rate for patients with measurable disease</b>	<b>N = 256</b>	<b>N = 245</b>
Overall Response Rate (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)
Abbreviations: CI, confidence interval; NR, not reached.		
<sup>a</sup> p-value estimated from one-sided log-rank test.		

**Figure 2** Kaplan-Meier Plot of Progression-Free Survival – MONALEESA-2 (Investigator Assessment, Intent-to-Treat Population)



**Figure 3** Kaplan-Meier plot of Overall Survival Curves – MONALEESA-2 (Intent-to-Treat Population)



#### MONALEESA-7: KISQALI in Combination with a Non-Steroidal Aromatase Inhibitor with or without Goserelin

*Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

MONALEESA-7 (NCT02278120) was a randomized (1:1), double-blind, placebo-controlled study of KISQALI plus either NSAI or tamoxifen and goserelin vs. placebo plus either a NSAI or tamoxifen and goserelin conducted in

pre/perimenopausal women (N = 672) with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.

Participants were randomized to receive KISQALI plus NSAI or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin, stratified according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease, and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin).

NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen 20 mg were given orally once daily on a continuous daily schedule, goserelin was administered as a sub-cutaneous injection on Day 1 of each 28-day cycle, with either KISQALI 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

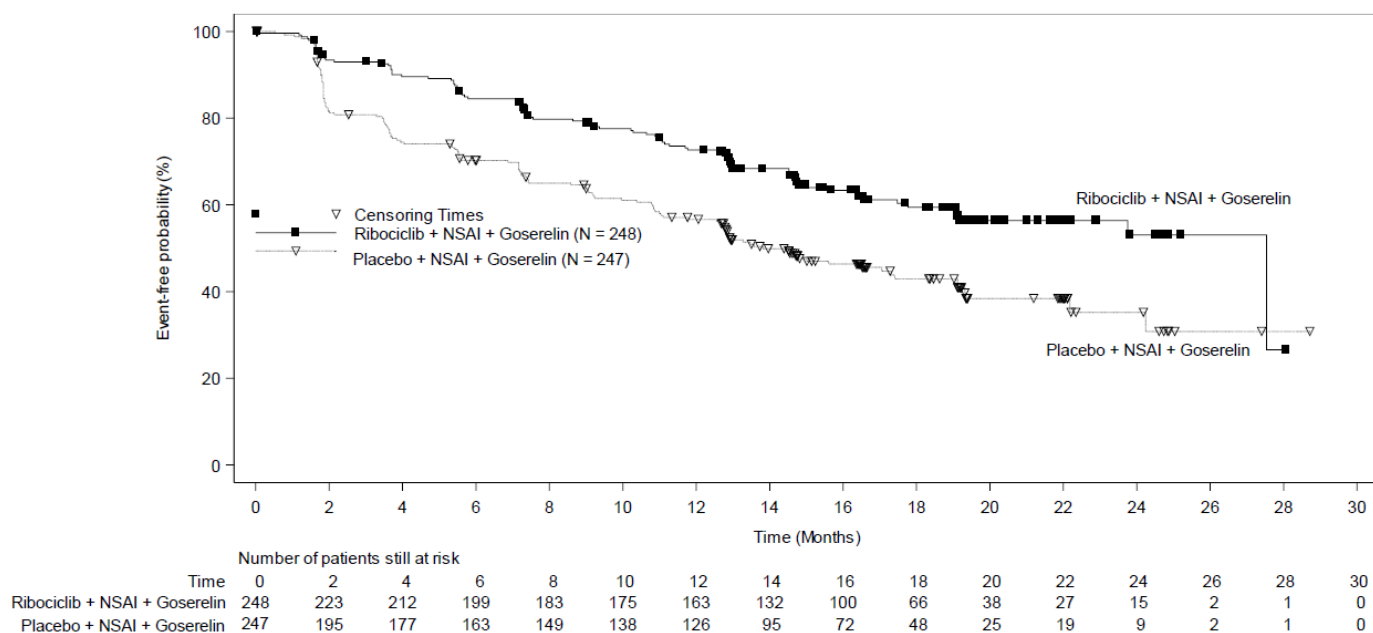
The median age was 44 years (range, 25 to 58). Patients were primarily White (58%), Asian (29%), or Black (3%). Nearly all patients (99%) had an ECOG performance status of 0 or 1. Of the 672 patients, 33% had received chemotherapy in the adjuvant vs. 18% in the neoadjuvant setting and 40% had received endocrine therapy in the adjuvant vs. 0.7% in the neoadjuvant setting prior to study entry. Forty percent (40%) of patients had *de novo* metastatic disease, 24% had bone-only disease, and 57% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms, and endocrine combination partner.

The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KISQALI or placebo with NSAI plus goserelin are summarized in Table 18, Figure 4, and Figure 5. Consistent results were observed in the stratification factor subgroups of disease site and prior chemotherapy for advanced disease.

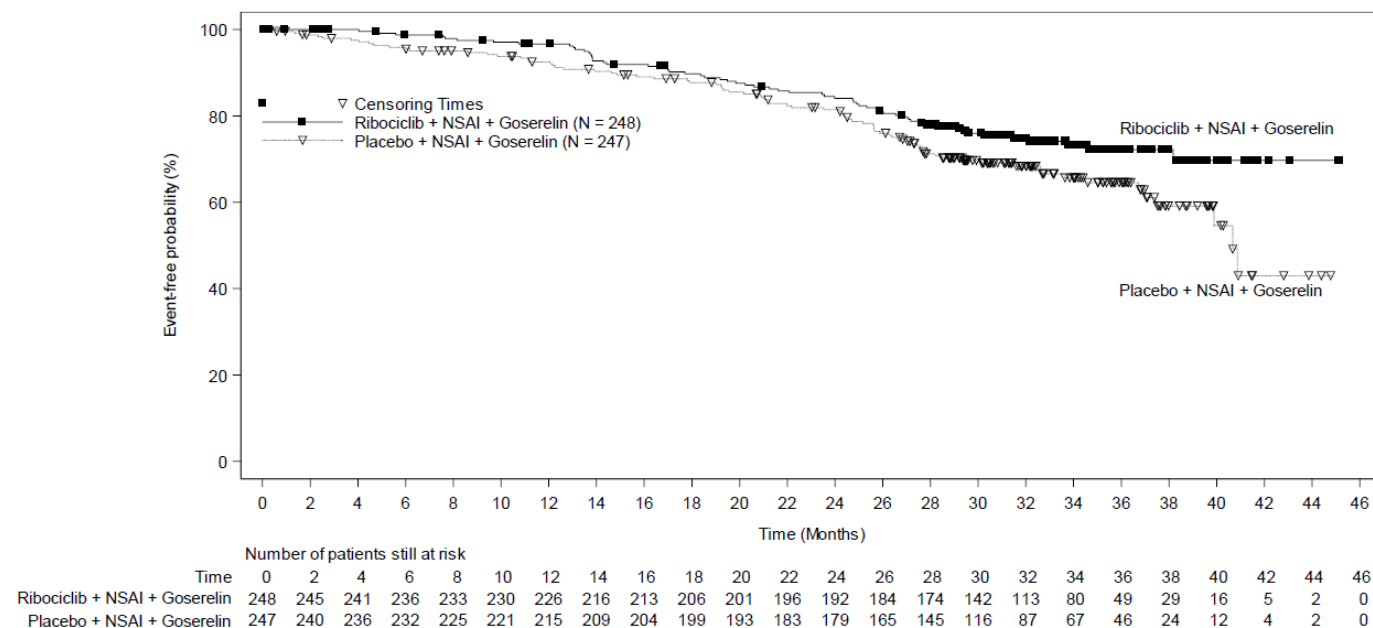
**Table 18: Efficacy Results – MONALEESA-7 (NSAI, Investigator Assessment)**

	<b>KISQALI + NSAI + Goserelin</b>	<b>Placebo + NSAI + Goserelin</b>
<b>Progression-Free Survival<sup>1</sup></b>	<b>N = 248</b>	<b>N = 247</b>
Events (n, %)	92 (37.1)	132 (53.4)
Median (months, 95% CI)	27.5 (19.1, NR)	13.8 (12.6, 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	
<b>Overall Survival</b>	<b>N = 248</b>	<b>N = 247</b>
Events (n, %)	61 (24.6)	80 (32.4)
Median (months, 95% CI)	NR (NR, NR)	40.7 (37.4, NR)
Hazard ratio (95% CI)	0.699 (0.501, 0.976)	
<b>Overall Response Rate for patients with measurable disease<sup>*,1</sup></b>	<b>N = 192</b>	<b>N = 199</b>
Overall Response Rate (95% CI)	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)
Abbreviations: CI, confidence interval; NR, not reached; NSAI, non-steroidal aromatase inhibitors.		
*Based on confirmed responses.		
<sup>1</sup> Investigator Assessment.		

**Figure 4** Kaplan-Meier Plot of Progression-Free Survival Curves – MONALEESA-7 (NSAI, Investigator Assessment)



**Figure 5** Kaplan-Meier Plot of Overall Survival - MONALEESA-7 (NSAI, Investigator Assessment)



#### COMPLEMENT-1: KISQALI in combination with Letrozole and Goserelin or Leuprolide

*Men with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

COMPLEMENT-1 (NCT 02941926) was an open-label, multicenter clinical study of ribociclib in combination with letrozole and goserelin or leuprolide for the treatment of adults with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease.

The study included 39 male patients who received KISQALI 600 mg orally once daily for 21 consecutive days followed by 7 days off; and letrozole 2.5 mg orally once daily for 28 days; and goserelin 3.6 mg as injectable subcutaneous implant or leuprolide 7.5 mg as intramuscular injection administered on Day 1 of each 28-day cycle. Patients were treated until disease progression or unacceptable toxicity occurred.

Male patients enrolled in this study had a median age of 62 years (range, 33 to 80). Of these patients, 39% were 65 years and older, including 10% aged 75 years and older. The male patients enrolled were White (72%), Asian (8%), and Black (3%), with 17% unknown. Nearly all male patients (97%) had an ECOG performance status of 0 or 1. The majority of male patients (97%) had 4 or less metastatic sites, which were primarily bone and visceral (69% each). Table 19 summarizes the efficacy results in male patients from COMPLEEMENT-1.

**Table 19: Efficacy Results in Male Patients<sup>1</sup> – COMPLEEMENT-1 (Investigator Assessment, Intent-to-Treat Population)**

	<b>KISQALI + Letrozole + Goserelin or Leuprolide</b>
<b>Overall Response Rate for patients with measurable disease<sup>*2</sup></b>	<b>N = 32</b>
Overall Response Rate (95% CI)	46.9 (29.1, 65.3)
<b>Duration of Response (DoR)<sup>3</sup></b>	<b>N = 15</b>
Median (months, 95% CI)	NR (21.3, NR)
Patients with DoR ≥12 months, n (%)	12 (80.0)
Abbreviations: CI, confidence interval, NR, not reached. <sup>*</sup> Based on confirmed responses. <sup>1</sup> Patients with measurable disease. <sup>2</sup> Investigator Assessment. <sup>3</sup> Patients with complete response or partial response.	

## 16 HOW SUPPLIED/STORAGE AND HANDLING

KISQALI FEMARA CO-PACK is dispensed in a carton for a total of 28 days of therapy.

Each carton contains individual ribociclib and letrozole drug products as follows:

### **KISQALI (ribociclib) Tablets:**

200 mg tablets.

Light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side.

### **FEMARA (letrozole) Tablets:**

2.5 mg tablets.

Dark yellow, round, slightly biconvex, with beveled edges, imprinted with the letters “FV” on one side and “CG” on the other side.

### **KISQALI FEMARA CO-PACK Cartons:**

- NDC 0078-0923-61 – Carton of 3 blister packs (63 tablets total) – each blister pack contains a 7-day supply of 21 tablets (200 mg per tablet) (600 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA
- NDC 0078-0916-61 – Carton of 3 blister packs (42 tablets total) – each blister pack contains a 7-day supply of 14 tablets (200 mg per tablet) (400 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA
- NDC 0078-0909-61 – Carton of 1 blister pack (21 tablets total) – each blister pack contains a 21-day supply of 21 tablets (200 mg per tablet) (200 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

Store at room temperature at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F).

Store in the original blister package in order to protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

For additional information on KISQALI and FEMARA, refer to the full prescribing information for each product.

### Interstitial Lung Disease/Pneumonitis

Advise patients to immediately report new or worsening respiratory symptoms [see *Warnings and Precautions* (5.1)].



### Severe Cutaneous Adverse Reactions

Inform patients of the signs and symptoms of severe cutaneous adverse reactions (e.g., skin pain/burning, rapidly-spreading skin rash, and/or mucosal lesions accompanied by fever or flu-like symptoms). Advise patients to contact their healthcare provider immediately if they develop signs and symptoms of severe cutaneous adverse reactions [see *Warnings and Precautions* (5.2)].

### QT Prolongation

Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately for signs or symptoms of QT prolongation [see *Warnings and Precautions* (5.3)].

### Hepatobiliary Toxicity

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

### 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 suggestion of infection [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.
- Advise females of reproductive potential to use effective contraception during KISQALI FEMARA CO-PACK therapy and for at least 3 weeks after the last dose. [see *Warnings and Precautions* (5.6), *Use in Specific Populations* (8.1, 8.3)].

### Lactation

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

### Drug Interactions

- Inform patients to avoid strong CYP3A inhibitors, strong CYP3A inducers, and drugs known to prolong the QT interval [see *Drug Interactions* (7.1, 7.2, 7.4)].

### Infertility

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

### Dosing

- Instruct patients to take the doses of KISQALI FEMARA CO-PACK at approximately the same time every day and to swallow tablets 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 KISQALI FEMARA CO-PACK may be taken with or without food [see *Dosage and Administration* (2.1)].

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East Hanover, New Jersey 07936

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**PATIENT INFORMATION**  
**KISQALI® FEMARA® CO-PACK** (kis kah' lee fe ma' ra koe' pak)  
(ribociclib tablets; letrozole tablets)  
co-packaged for oral use

**What is the most important information I should know about KISQALI FEMARA CO-PACK?**

**KISQALI FEMARA CO-PACK may cause serious side effects, including:**

- **Lung problems.** KISQALI may cause severe or life-threatening inflammation of the lungs during treatment that may lead to death. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
  - trouble breathing or shortness of breath
  - cough with or without mucus
  - chest pain
- **Severe skin reactions.** Tell your healthcare provider or get medical help right away if you get severe rash or rash that keeps getting worse, reddened skin, flu-like symptoms, skin pain or burning, blistering of the lips, eyes or mouth, blisters on the skin or skin peeling, with or without fever.
- **Heart rhythm problems (QT prolongation).** KISQALI FEMARA CO-PACK can cause a heart problem known as QT prolongation. This condition can cause an abnormal heartbeat and may lead to death.
  - Your healthcare provider should check your heart and do blood tests before and during treatment with KISQALI FEMARA CO-PACK.
  - **Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you feel dizzy or faint.**
- **Liver problems.** KISQALI FEMARA CO-PACK can cause serious liver problems. Your healthcare provider will do blood tests to check your liver before and during treatment with KISQALI FEMARA CO-PACK. Tell your healthcare provider right away if you get any of the following signs and symptoms of liver problems:
  - yellowing of your skin or the whites of your eyes (jaundice)
  - dark or brown (tea-colored) urine
  - feeling very tired
  - loss of appetite
  - pain on the upper right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal
- **Low white blood cell counts (neutropenia).** Low white blood cell counts are very common during treatment with KISQALI FEMARA CO-PACK and may result in infections that may be severe. Your healthcare provider should check your white blood cell counts before and during treatment with KISQALI FEMARA CO-PACK. Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections, such as fever and chills.

Your healthcare provider may tell you to decrease your dose, temporarily stop or completely stop taking KISQALI if you develop certain serious side effects during treatment with KISQALI.

See “**What are the possible side effects of KISQALI FEMARA CO-PACK?**” for more information about side effects.

**What is KISQALI FEMARA CO-PACK?**

KISQALI FEMARA CO-PACK is a prescription medicine used to treat adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer:

- in combination with aromatase inhibitor for stage II and III early breast cancer with a high risk of coming back.
- That has gotten worse or has spread to other parts of the body (advanced or metastatic breast cancer) in combination with an aromatase inhibitor as the first endocrine-based therapy.

KISQALI FEMARA CO-PACK contains 2 different types of medicines:

- The violet tablet contains the medicine KISQALI (ribociclib).
- The yellow tablet contains the medicine FEMARA (letrozole).

It is not known if KISQALI FEMARA CO-PACK is safe and effective in children.

**Do not take KISQALI FEMARA CO-PACK if you are allergic to letrozole or any of the ingredients of FEMARA.**

See the end of this Patient Information for a list of the ingredients in KISQALI FEMARA CO-PACK.

**Before taking KISQALI FEMARA CO-PACK, tell your healthcare provider about all your medical conditions, including if you:**

- have any heart problems, including heart failure, irregular heartbeats, and QT prolongation
- have ever had a heart attack
- have a slow heartbeat (bradycardia)
- have high blood pressure that is not controlled
- have decreased thyroid gland function (hypothyroidism)

- have problems with the amount of potassium, calcium, phosphorus, or magnesium in your blood
- have fever, chills, or any other signs or symptoms of infection
- have liver problems
- have kidney problems
- are pregnant, or plan to become pregnant. KISQALI FEMARA CO-PACK can harm your unborn baby.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with KISQALI FEMARA CO-PACK.
  - Females who are able to become pregnant and who take KISQALI FEMARA CO-PACK should use effective birth control during treatment and for at least 3 weeks after the last dose of KISQALI FEMARA CO-PACK.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if KISQALI FEMARA CO-PACK passes into your breast milk. Do not breastfeed during treatment with KISQALI FEMARA CO-PACK and for at least 3 weeks after the last dose of KISQALI FEMARA CO-PACK.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. KISQALI FEMARA CO-PACK and other medicines may affect each other causing side effects. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

#### **How should I take KISQALI FEMARA CO-PACK?**

- Take KISQALI FEMARA CO-PACK exactly as your healthcare provider tells you.
- Do not change your dose or stop taking KISQALI FEMARA CO-PACK without talking to your healthcare provider.
- KISQALI FEMARA CO-PACK comes in a carton that contains enough KISQALI tablets and FEMARA tablets for 28 days of treatment.
- Take KISQALI FEMARA CO-PACK each day at about the same time, preferably in the morning.
- Take KISQALI FEMARA CO-PACK with food or without food.
- Swallow KISQALI tablets and FEMARA tablets whole. Do not chew, crush or split tablets before swallowing them.
- Do not take any KISQALI tablets and FEMARA tablets that are broken, cracked, or that look damaged.
- If you miss a dose or vomit after taking a dose of KISQALI FEMARA CO-PACK, do not take another dose on that day. Take your next dose at your regular time.

#### **What are the possible side effects of KISQALI FEMARA CO-PACK?**

**KISQALI FEMARA CO-PACK may cause serious side effects.**

- See "**What is the most important information I should know about KISQALI FEMARA CO-PACK?**"

**The most common side effects of KISQALI in people with early breast cancer include:**

- |                                     |                             |
|-------------------------------------|-----------------------------|
| • decreased white blood cell counts | • decreased platelet counts |
| • decreased red blood cell counts   | • nausea                    |
| • increased liver function tests    | • headache                  |
| • infections                        | • tiredness                 |
| • increased kidney function test    |                             |

**The most common side effects of KISQALI FEMARA CO-PACK in people with advanced or metastatic breast cancer include:**

- |                                     |                             |                |                                  |
|-------------------------------------|-----------------------------|----------------|----------------------------------|
| • decreased white blood cell counts | • infections                | • headache     | • rash                           |
| • decreased red blood cell counts   | • nausea                    | • hair loss    | • increased kidney function test |
| • increased liver function tests    | • tiredness                 | • vomiting     | • stomach-area (abdomen) pain    |
|                                     | • decreased platelet counts | • back pain    |                                  |
|                                     | • diarrhea                  | • constipation |                                  |
|                                     |                             | • cough        |                                  |

KISQALI FEMARA CO-PACK may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if this is a problem for you.

These are not all of the possible side effects of KISQALI FEMARA CO-PACK.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store KISQALI FEMARA CO-PACK?**

- Store KISQALI FEMARA CO-PACK at room temperature between 68°F to 77°F (20°C to 25°C).
- Store KISQALI FEMARA CO-PACK in the original blister package in order to protect from moisture.

**Keep KISQALI FEMARA CO-PACK and all medicines out of the reach of children.**

**General information about the safe and effective use of KISQALI FEMARA CO-PACK.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KISQALI FEMARA CO-PACK for a condition for which it was not prescribed. Do not give KISQALI FEMARA CO-PACK to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about KISQALI FEMARA CO-PACK that is written for health professionals.

**What are the ingredients in KISQALI FEMARA CO-PACK?**

**KISQALI (ribociclib) tablets:**

**Active ingredient:** ribociclib

**Inactive ingredients:** colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide, and xanthan gum

**FEMARA (letrozole) tablets:**

**Active ingredient:** letrozole

**Inactive ingredients:** colloidal silicon dioxide, ferric oxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide

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For more information, go to [www.KISQALI.com](http://www.KISQALI.com) or call 1-888-669-6682.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: September 2025

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