

## 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

### INDICATIONS AND USAGE

KISQALI FEMARA CO-PACK, a co-packaged product containing ribociclib, a kinase inhibitor, and letrozole, an aromatase inhibitor, is indicated as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. (1)

### DOSAGE AND ADMINISTRATION

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

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

None. (4)

### WARNINGS AND PRECAUTIONS

- 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 at the beginning of the second cycle, and as clinically indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated. (2.2, 5.1)

- Hepatobiliary toxicity: Increases in serum transaminase 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, 5.2)
- 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, 5.3)
- Embryo-Fetal toxicity: Can cause fetal harm when administered to pregnant women. Advise women of child-bearing potential of the potential risk to a fetus and to use effective contraception during therapy. (5.4, 8.1, 8.3)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq$  20%) are neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back 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 sensitive 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: 5/2017

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosing and Administration

The KISQALI FEMARA CO-PACK is comprised of ribociclib tablets copackaged with letrozole tablets, to provide a 28-day treatment regimen.

The KISQALI FEMARA CO-PACK should be coadministered, with or without food, as follows:

- **KISQALI:** The recommended starting dose for KISQALI is 600 mg (three 200 mg tablets) taken orally, once daily for 21 consecutive days followed by 7 days off KISQALI treatment resulting in a complete cycle of 28 days.
- **FEMARA:** 2.5 mg (one tablet) taken once daily throughout the 28-day cycle.

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.

For additional information on KISQALI® and FEMARA®, refer to the Full Prescribing Information 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
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 further dose reduction below 200 mg/day is required, discontinue KISQALI

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

**Table 2: 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>	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 (CBC) 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.				
*Grade 3 neutropenia with single episode of fever >38.3°C (or) above 38°C for more than one hour and/or concurrent infection. Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events. ANC = absolute neutrophil count; LLN = lower limit of normal				

**Table 3: Dose Modification and Management of KISQALI for Hepatobiliary Toxicity**

	<b>Grade 1</b> (> ULN – 3 x ULN)	<b>Grade 2</b> (>3 to 5 x ULN)	<b>Grade 3</b> (>5 to 20 x ULN)	<b>Grade 4</b> (>20 x ULN)
<b>AST and/or ALT elevations from baseline*, WITHOUT increase in total bilirubin above 2 x ULN</b>	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, 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>	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, more frequent monitoring is recommended.				
*Baseline = prior to treatment initiation. Grading according to CTCAE Version 4.03. ULN = upper limit of normal AST = aspartate aminotransferase; ALT = alanine aminotransferase				

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

<b>ECGs with QTcF &gt; 480 msec</b>	<ol style="list-style-type: none"> <li>1. Interrupt KISQALI Treatment</li> <li>2. If QTcF prolongation resolves to &lt; 481 msec, resume treatment at the same dose level;</li> <li>3. If QTcF <math>\geq</math> 481 msec recurs, interrupt dose until QTcF resolves to &lt; 481 msec; then resume KISQALI at next lower dose level.</li> </ol>
<b>ECGs with QTcF &gt; 500 msec</b>	<ol style="list-style-type: none"> <li>1. Interrupt KISQALI treatment if QTcF greater than 500 msec on at least 2 separate ECGs (within the same visit).</li> <li>2. If QTcF prolongation resolves to &lt; 481 msec, resume treatment at the next lower dose level</li> </ol> <p>Permanently discontinue KISQALI if QTcF interval prolongation is either greater than 500 msec or greater than 60 msec change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia.</p>

Electrocardiograms (ECGs) should be assessed prior to initiation of treatment.  
Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated.  
In case of (QTcF) prolongation at any given time during treatment, more frequent ECG monitoring is recommended.

**Table 5: 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 $\leq$ 1 then resume KISQALI at same dose level. If Grade 3 recurs, resume KISQALI at the next lower dose level.	Discontinue KISQALI.

\*Excluding neutropenia, hepatobiliary toxicity and QT interval prolongation.  
Grading according to CTCAE Version 4.03.

### 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 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)* and *Clinical Pharmacology (12.3)*].

### Dose Modification for Hepatic Impairment

No dose adjustment of KISQALI is necessary in patients with mild hepatic impairment (Child-Pugh class A). The recommended starting dose is 400 mg KISQALI once daily for patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) [see *Clinical Pharmacology (12.3)*].

No dose adjustment of FEMARA is necessary in patients with 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)*].

## 3 DOSAGE FORMS AND STRENGTHS

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

- Tablets 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.
- Tablets 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

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms (90% CI: 21.6, 24.1)) at the mean steady-state  $C_{max}$  following administration at 600 mg once daily dose [see *Clinical Pharmacology (12.2)*]. In Study 1 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. On 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 [see *Adverse Reactions (6)*].

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI FEMARA CO-PACK only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

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

Avoid the use of KISQALI FEMARA CO-PACK in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI FEMARA CO-PACK with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval [see *Drug Interactions (7.4)*, *Clinical Pharmacology (12.3)*].

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)* and *Drug Interactions (7.4)*].

### 5.2 Hepatobiliary Toxicity

In Study 1, increases in transaminases were observed. Grade 3 or 4 increases in ALT (10% versus 1%) and AST (7% versus 2%) were reported in the KISQALI FEMARA CO-PACK and placebo arms respectively.

Among the patients who had Grade  $\geq 3$  ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI FEMARA CO-PACK treatment group. The median time to resolution to Grade  $\leq 2$  was 24 days in the KISQALI plus letrozole treatment group.

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 occurred in 4 (1%) patients in Study 1 and all patients recovered after discontinuation of KISQALI.

Perform LFTs before initiating therapy with 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 3 (Dose Modification and Management for Hepatobiliary toxicity) [see *Dosage and Administration (2.2)*]. Recommendations for patients who have elevated AST/ALT Grade  $\geq 3$  at baseline have not been established.

### 5.3 Neutropenia

In Study 1, neutropenia was the most frequently reported adverse reaction (75%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 60% of patients receiving KISQALI FEMARA CO-PACK. Among

the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade  $\geq 2$  neutropenia was 16 days. The median time to resolution of Grade  $\geq 3$  (to normalization or Grade  $< 3$ ) was 15 days in the KISQALI FEMARA CO-PACK treatment group. Febrile neutropenia was reported in 1.5% of patients receiving KISQALI FEMARA CO-PACK. Treatment discontinuation due to neutropenia was 0.9%.

Perform 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.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 2 [*see Dosage and Administration (2.2)*].

#### **5.4 Embryo-Fetal Toxicity**

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.

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 (MHRD) on a  $\text{mg}/\text{m}^2$  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) and Clinical Pharmacology (12.1)*].

### **6 ADVERSE REACTIONS**

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

- QT Interval Prolongation [*see Warnings and Precautions (5.1)*]
- Hepatobiliary Toxicity [*see Warnings and Precautions (5.2)*]
- Neutropenia [*see Warnings and Precautions (5.3)*]

#### **6.1 Clinical Trial 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 safety data reported below are based on Study 1 (MONALEESA-2), a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for  $\geq 12$  months.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving KISQALI plus letrozole and 2% in patients receiving placebo plus letrozole. The most common ARs leading to treatment discontinuation of both KISQALI and letrozole in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), and vomiting (2%). Antiemetics and antidiarrhea medications were used to manage symptoms as clinically indicated.

On-treatment deaths, regardless of causality, were reported in three cases (0.9%) of KISQALI plus letrozole treated patients vs. one case (0.3%) of placebo plus letrozole treated patients. Causes of death on KISQALI plus letrozole included one case each of the following: progressive disease, death (cause unknown), and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation).

The most common ARs (reported at a frequency  $\geq 20\%$ ) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain.

The most common Grade 3/4 ARs (reported at a frequency  $> 2\%$ ) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

ARs and laboratory abnormalities occurring in patients in Study 1 are listed in Table 6 and Table 7, respectively.

**Table 6: Adverse Reactions Occurring in  $\geq 10\%$  and  $\geq 2\%$  higher than Placebo Arm in Study 1 (All Grades)**

	KISQALI + letrozole			Placebo + letrozole		
	All Grades	N=334		All Grades	N=330	
Adverse drug reactions	%	Grade 3 %	Grade 4 %	%	Grade 3 %	Grade 4 %
<b>Infections and Infestations</b>						
Urinary tract infection	11	1	0	8	0	0
<b>Blood and lymphatic system disorders</b>						
Neutropenia	75	50	10	5	1	0
Leukopenia	33	20	1	1	<1	0
Anemia	18	1	<1	5	1	0
Lymphopenia	11	6	1	2	1	0
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	19	2	0	15	<1	0
<b>Nervous system disorders</b>						
Headache	22	<1	0	19	<1	0
Insomnia	12	<1	0	9	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Dyspnea	12	1	0	9	1	0
<b>Musculoskeletal and connective tissue disorders</b>						
Back pain	20	2	0	18	<1	0
<b>Gastrointestinal disorders</b>						
Nausea	52	2	0	29	1	0
Diarrhea	35	1	0	22	1	0
Vomiting	29	4	0	16	1	0
Constipation	25	1	0	19	0	0
Stomatitis	12	<1	0	7	0	0
Abdominal pain	11	1	0	8	0	0
<b>Skin and subcutaneous tissue disorders</b>						
Alopecia	33	0	0	16	0	0
Rash	17	1	0	8	0	0
Pruritus	14	1	0	6	0	0
<b>General disorders and administration site conditions</b>						
Fatigue	37	2	<1	30	1	0
Pyrexia	13	<1	0	6	0	0
Edema peripheral	12	0	0	10	0	0
<b>Investigations</b>						
Abnormal liver function tests <sup>1</sup>	18	8	2	6	2	0

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

<sup>1</sup> abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased**Table 7: Laboratory Abnormalities Occurring in  $\geq 10\%$  of Patients in Study 1**

	KISQALI + letrozole			Placebo + letrozole		
	All Grades	N=334		All Grades	N=330	
Laboratory parameters	%	Grade 3 %	Grade 4 %	%	Grade 3 %	Grade 4 %
<b>HEMATOLOGY</b>						
Leukocyte count decreased	93	31	3	29	1	<1
Neutrophil count decreased	93	49	11	24	1	<1

	KISQALI + letrozole			Placebo + letrozole		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	N=334			N=330		
<b>Laboratory parameters</b>	%	%	%	%	%	%
Hemoglobin decreased	57	2	0	26	1	0
Lymphocyte count decreased	51	12	2	22	3	1
Platelet count decreased	29	1	< 1	6	0	< 1
<b>CHEMISTRY</b>						
Alanine aminotransferase increased	46	8	2	36	1	0
Aspartate aminotransferase increased	44	6	1	32	2	0
Creatinine increased	20	1	0	6	0	0
Phosphorous decreased	13	5	1	4	1	0
Potassium decreased	11	1	1	7	1	0

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

#### *Bone Effects:*

In Study 1, 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.

## **7 DRUG INTERACTIONS**

### **Ribociclib**

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

##### *CYP3A4 Inhibitors*

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold [see *Clinical Pharmacology (12.3)*]. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

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)*].

Instruct patients to avoid pomegranates or pomegranate juice, grapefruit, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib [see *Patient Counseling Information (17)*].

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

##### *CYP3A4 Inducers*

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% [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 (e.g., phenytoin, rifampin, carbamazepine and St. John's Wort (*Hypericum perforatum*)).

#### **7.3 Effect of KISQALI on Other Drugs**

*CYP3A substrates with narrow therapeutic index:*



Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone [*see Clinical Pharmacology (12.3)*]. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

#### **7.4 Drugs That Prolong the QT Interval**

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron (i.v)) [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

## **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. Advise pregnant women of the potential risk to a fetus.

In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of postimplantation 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*).

In animal reproduction studies, administration of letrozole to pregnant animals during organogenesis resulted 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 maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis (*see Data*).

The background risk of major birth defects 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 maximum recommended human dose 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 maximum recommended human dose 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 maximum recommended human dose 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 maximum recommended human dose 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, sternbrae, 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 maximum recommended human dose 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

### Pregnancy Testing

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)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with KISQALI FEMARA CO-PACK.

### Contraception

#### *Females*

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)*]. 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 has 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 334 patients who received KISQALI plus letrozole in Study 1, 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 these patients and younger patients.

#### **8.6 Hepatic Impairment**

No dose adjustment of KISQALI is necessary in patients with mild hepatic impairment (Child-Pugh class A). The recommended starting dose is 400 mg KISQALI once daily for patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) [see *Clinical Pharmacology (12.3)*].

No dose adjustment of FEMARA is necessary in patients with 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)*].

### **10 OVERDOSAGE**

There were no known cases of overdose with ribociclib and letrozole in Study 1. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

Refer to the Full Prescribing Information of FEMARA for additional overdose information.

### **11 DESCRIPTION**

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

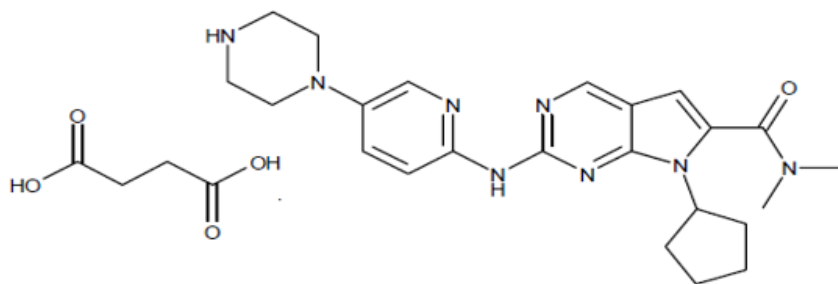
#### **Ribociclib:**

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  $C_{23}H_{30}N_8O \cdot C_4H_6O_4$  and the molecular weight is 552.64 g/mole [*Free base: 434.55 g/mol*].

The chemical structure of ribociclib is shown below:



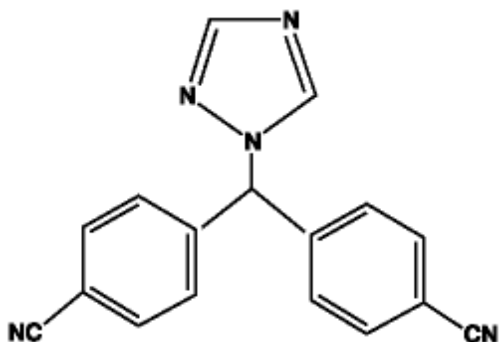
KISQALI film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating 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, empirical formula  $C_{17}H_{11}N_5$ , and a melting range of 184°C to 185°C.

The chemical name of letrozole is 4,4'-(1H-1,2,4-Triazol-1ylmethylene)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 play a crucial role in 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 leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell 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 vivo* studies, using patient-derived estrogen receptor positive breast cancer xenograft models, combination of ribociclib and antiestrogen (e.g. letrozole) resulted in increased tumor growth inhibition compared to each drug alone.

## 12.2 Pharmacodynamics

### Ribociclib

#### *Cardiac Electrophysiology*

Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 267 patients treated with ribociclib at doses ranging from 50 to 1200 mg, including 193 patients treated with ribociclib 600 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF was 22.9 ms (90% CI: 21.6, 24.1) at the mean observed  $C_{max}$  at steady-state following administration at the recommended 600 mg dose [see *Warnings and Precautions (5.1)*].

### 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, 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 LH and FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH levels, T3 uptake, and T4 levels.

## 12.3 Pharmacokinetics

Ribociclib exhibited over-proportional increases in exposure (peak plasma concentrations ( $C_{max}$ ) and area under the time concentration curve (AUC)) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range 0.972 to 6.40).

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 and Distribution

#### Ribociclib

The time to reach  $C_{max}$  ( $T_{max}$ ) following ribociclib administration was between 1 and 4 hours.

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady-state ( $V_{ss}/F$ ) was 1090 L based on population PK analysis.

*Food Effect:* Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI film-coated 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 effect on the rate and extent of absorption of ribociclib ( $C_{max}$  GMR: 1.00; 90% CI: 0.898, 1.11;  $AUC_{inf}$  GMR: 1.06; 90% CI: 1.01, 1.12).

## **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**

In vitro and in vivo studies indicated 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. Phase II conjugates of ribociclib Phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. 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 (pharmacological and safety) 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 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts ( $\leq 3\%$  of the administered dose).

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The geometric mean apparent plasma terminal half-life (T<sub>1/2</sub>) of ribociclib ranged from 29.7 to 54.7 hours and geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects.

Ribociclib is eliminated mainly via feces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of radio-labeled ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; feces was the major route of excretion (69%), with 23% of the dose recovered in urine.

## **Letrozole**

Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzotrile) 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**

Based on a pharmacokinetic trial in patients with hepatic impairment, mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (Child-Pugh class B; geometric mean ratio [GMR]: 1.50 for C<sub>max</sub>; 1.32 for AUC<sub>inf</sub>) and severe (Child-Pugh class C; GMR: 1.34 for C<sub>max</sub>; 1.29 for AUC<sub>inf</sub>) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study.

#### **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 classification 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 classification C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had twofold 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**

The pharmacokinetics of ribociclib in patients with severe renal impairment ( $\text{eGFR} < 30 \text{ mL/min/1.73m}^2$ ) is unknown. Mild ( $60 \text{ mL/min/1.73m}^2 \leq \text{eGFR} < 90 \text{ mL/min/1.73m}^2$ ) and moderate ( $30 \text{ mL/min/1.73m}^2 \leq \text{eGFR} < 60 \text{ mL/min/1.73m}^2$ ) renal impairment had no effect on the exposure of ribociclib based on a population PK analysis.

##### **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.

##### **Additional pharmacokinetic information on ribociclib:**

The pharmacokinetics of ribociclib was investigated in patients with advanced cancer following oral daily doses ranging from 50 mg to 1200 mg. Healthy subjects received single oral doses of 400 or 600 mg or repeated daily oral doses (8 days) at 400 mg.

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

Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib.

##### Drug Interaction Studies

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

*CYP3A inhibitors:* A drug interaction trial in healthy subjects was conducted with ritonavir (a strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100 mg twice a day for 14 days) increased ribociclib  $C_{\text{max}}$  and  $\text{AUC}_{\text{inf}}$  by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose.  $C_{\text{max}}$  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  $C_{\text{max}}$  and AUC by 1.3-fold and 1.9-fold, respectively.

*CYP3A inducers:* A drug interaction trial in healthy subjects was conducted with rifampicin (a strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib  $C_{\text{max}}$  and  $\text{AUC}_{\text{inf}}$  by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803  $C_{\text{max}}$  increased 1.7-fold and  $\text{AUC}_{\text{inf}}$  decreased by 27%, respectively. A moderate CYP3A inducer (efavirenz) is predicted to decrease ribociclib  $C_{\text{max}}$  and AUC by 37% and 60%, respectively.

##### *Drugs That Are Affected By KISQALI*

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

*Gastric pH-elevating agents:* Coadministration of ribociclib with drugs that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not identified in a population PK analysis and was not predicted using physiology based PK models.

*Letrozole:* Data from a clinical trial in patients with breast cancer and population PK analysis 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.

#### *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 KISQALI 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 KISQALI has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. KISQALI 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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Ribociclib**

Carcinogenesis studies have not been conducted with ribociclib.

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.

Fertility studies in animals have 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 maximum recommended human dose 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 maximum recommended human dose 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 (CHO K1 and CCL 61 Chinese hamster ovary 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 maximum recommended human dose 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<sub>max</sub>).

## 14 CLINICAL STUDIES

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

A total of 668 patients were randomized to receive either KISQALI and letrozole (n= 334) or placebo and letrozole (n= 334), 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).

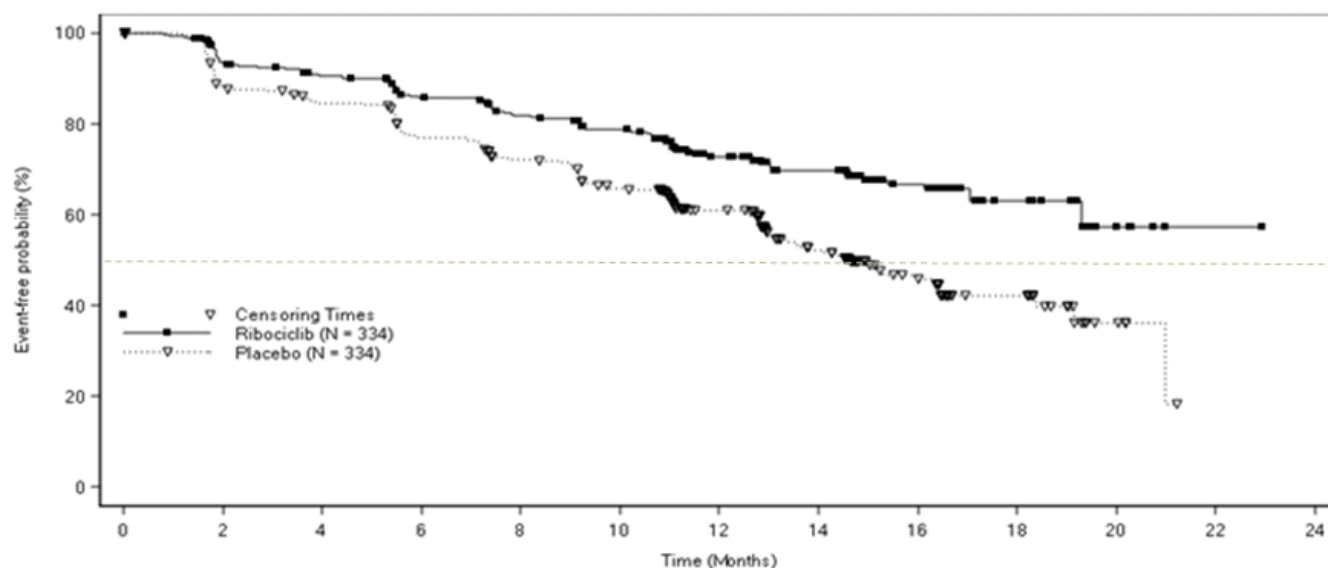
Patients enrolled in Study 1 had a median age of 62 years (range 23 to 91) and 45% of patients were older than 65. The majority of patients were White (82%), and all patients had an ECOG performance status of 0 or 1. A total of 47% of patients had received chemotherapy and 51% had received antihormonal 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 from Study 1 are summarized in Table 8 and Figure 1. The results shown are from a pre-planned interim efficacy analysis of PFS. Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment. At the time of the PFS analysis, 6.5% of patients had died, and overall survival data were immature.

**Table 8: Efficacy Results – Study 1 (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 (%)	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 to 0.720)	
p-value	< 0.0001 <sup>a</sup>	
<b>Overall Response Rate</b>	<b>N=256</b>	<b>N=245</b>
Patients with measurable disease (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)
<sup>a</sup> p-value estimated from one-sided log-rank test NR = not reached		

**Figure 1: Kaplan-Meier Progression Free Survival Curves – Study 1 (Intent-to-Treat Population)**



## 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 - 3 Blister packs, containing 21 tablets (200 mg per tablet) (600 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA
- NDC 0078- 0916-61 - 3 Blister packs, containing 14 tablets (200 mg per tablet) (400 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA
- NDC 0078- 0909-61 - 1 Blister pack, containing 21 tablets (200 mg per tablet) (200 mg daily dose) of KISQALI plus one 28-tablet count bottle of FEMARA

Store KISQALI FEMARA CO-PACK at 20°C to 25°C (68°F to 77°F). Store in the original package.

## 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.

### *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 (5.1)].

### *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 (5.2)*].

### *Neutropenia*

Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any suggestion of infection [see *Warnings and Precautions (5.3)*].

### *Embryo-Fetal Toxicity*

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during KISQALI FEMARA CO-PACK therapy and for at least 3 weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with KISQALI FEMARA CO-PACK [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)*].

### *Lactation*

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

### *Drug Interactions*

- Inform patients to avoid pomegranate or pomegranate juice, and grapefruit or grapefruit juice while taking KISQALI FEMARA CO-PACK [see *Drug Interactions (7.1)*].
- 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)*].

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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:**

- **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 you start and while you take 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 when taking 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 as the first hormonal based therapy to treat women who have gone through menopause with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has spread to other parts of the body (metastatic).
- 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.

**Before you take KISQALI FEMARA CO-PACK, tell your healthcare provider about all of your medical condition, 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 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
- 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 of 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 unless your healthcare provider tells you.
- 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.
- You may 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.
- If you take too much KISQALI FEMARA CO-PACK, call your healthcare provider right away or go to the nearest hospital emergency room.

### What should I avoid while taking KISQALI FEMARA CO-PACK?

- Avoid eating pomegranate or grapefruit and avoid drinking pomegranate or grapefruit juice during treatment with KISQALI FEMARA CO-PACK since these may increase the amount of KISQALI in your blood.

### 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 FEMARA CO-PACK include:

- nausea
- diarrhea
- vomiting
- headache
- tiredness
- hair loss
- constipation
- back pain

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 you have concerns about fertility.

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 68°F to 77°F (20°C to 25°C).
- Keep KISQALI FEMARA CO-PACK in its original container.

#### 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 1-844-KISQALI (1-844-547-7254).