HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KISQALI® (ribociclib) tablets, for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------

KISQALI is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. (1)

----------DOSAGE AND ADMINISTRATION----------

KISQALI tablets are taken orally with or without food in combination with letrozole. (2)

- Recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment. (2.1)
- Dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 200 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. 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. 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. Advise patients of 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 ≥ 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.

----------DRUG INTERACTIONS----------

- CYP3A4 Inhibitors: Avoid concomitant use of KISQALI with strong CYP3A inhibitors. If strong inhibitors cannot be avoided, reduce KISQALI dose. (2.2, 7.1)
- CYP3A4 Inducers: Avoid concomitant use of KISQALI 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. (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: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Administration

The recommended dose of KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. KISQALI can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Coadminister KISQALI with letrozole 2.5 mg taken once daily throughout the 28-day cycle. Refer to the full prescribing information of letrozole. For dosing and administration with other aromatase inhibitors refer to the applicable full prescribing information.

Patients should take their dose of KISQALI and letrozole 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. KISQALI 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.

2.2 Dose Modifications

Dose Modifications for Adverse Reactions

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

Table 1: Recommended Dose Modification for Adverse Reactions

Level	KISQALI	
	Dose	**Number of Tablets**
Starting dose	600 mg/day	three 200 mg tablets
First dose reduction	400 mg/day	two 200 mg tablets
Second dose reduction	200 mg/day*	one 200 mg tablet

*If further dose reduction below 200 mg/day is required, discontinue the treatment.

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

Table 2: Dose Modification and Management for Neutropenia

	Grade 1 or 2 (ANC 1000/mm^3 – <LLN)	**Grade 3** (ANC 500 - <1000/mm^3)	**Grade 3 febrile* neutropenia**	**Grade 4** (ANC <500/mm^3)
Neutropenia	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 for Hepatobiliary Toxicity

	Grade 1 (> ULN – 3 x ULN)	**Grade 2** (>3 to 5 x ULN)	**Grade 3** (>5 to 20 x ULN)	**Grade 4** (>20 x ULN)
AST and/or ALT elevations from baseline*, WITHOUT increase in total bilirubin above 2 x ULN	No dose adjustment is required.	Baseline* at < Grade 2: Dose interruption until recovery to ≤ baseline grade, then resume KISQALI at same dose level. If Grade 2 recurs, resume KISQALI at next lower dose level. --- Baseline* at Grade 2: 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
Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis	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 for QT Prolongation

ECGs with QTcF > 480 msec	1. Interrupt KISQALI Treatment 2. If QTcF prolongation resolves to < 481 msec, resume treatment at the same dose level; 3. If QTcF ≥ 481 msec recurs, interrupt dose until QTcF resolves to < 481 msec; then resume KISQALI at next lower dose level.
ECGs with QTcF > 500 msec	1. Interrupt KISQALI treatment if QTcF greater than 500 msec on at least 2 separate ECGs (within the same visit). 2. If QTcF prolongation resolves to < 481 msec, resume treatment at the next lower dose level 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.
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 for Other Toxicities*

	Grade 1 or 2	Grade 3	Grade 4
Other toxicities	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 neutropenia, hepatobiliary toxicity and QT interval prolongation.
Grading according to 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 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 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 Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Review the Full Prescribing Information for the aromatase inhibitor for dose modifications related to hepatic impairment.

3 DOSAGE FORMS AND STRENGTHS

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.

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 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 therapy *[see Dosage and Administration (2.2)]*.

Avoid the use of KISQALI 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 with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval *[see 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 and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI plus letrozole treatment group. The median time to resolution to Grade ≤ 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. 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 ≥ 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 plus letrozole. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 15 days in the KISQALI plus letrozole treatment group.

Febrile neutropenia was reported in 1.5% of patients receiving KISQALI and letrozole. Treatment discontinuation due to neutropenia was 0.9%.

Perform CBC before initiating therapy with KISQALI. 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 mechanism of action, KISQALI 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). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Population (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 ≥ 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 KISQALI in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), 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 ≥ 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 ≥ 10% and ≥ 2% higher than Placebo Arm in Study 1 (All Grades)

	KISQALI + letrozole			Placebo + letrozole		
	N=334			N=330		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Urinary tract infection	11	1	0	8	0	0
Blood and lymphatic system disorders						
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
Metabolism and nutrition disorders						
Decreased appetite	19	2	0	15	<1	0
Nervous system disorders						
Headache	22	<1	0	19	<1	0
Insomnia	12	<1	0	9	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	0	9	1	0
Musculoskeletal and connective tissue disorders						
Back pain	20	2	0	18	<1	0
Gastrointestinal disorders						
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
Skin and subcutaneous tissue disorders						
Alopecia	33	0	0	16	0	0
Rash	17	1	0	8	0	0
Pruritus	14	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	<1	30	1	0
Pyrexia	13	<1	0	6	0	0
Edema peripheral	12	0	0	10	0	0
Investigations						
Abnormal liver function tests[1]	18	8	2	6	2	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1]abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

Table 7: Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1

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

7 DRUG INTERACTIONS

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 mechanism of action, KISQALI 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 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]*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk 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

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 13th 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.

8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data

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.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, KISQALI 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.

Contraception

Females

Based on animal studies, KISQALI 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 and for at least 3 weeks after the last dose.

Infertility

Males

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

8.4 Pediatric Use

The safety and efficacy of KISQALI in pediatric patients has not been established.

8.5 Geriatric Use

Of 334 patients who received KISQALI in Study 1, 150 patients (45%) were ≥65 years of age and 35 patients (11%) were ≥75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.2)]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild 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 (geometric mean ratio [GMR]: 1.50 for C_{max}; 1.32 for AUC_{inf}) and severe (GMR: 1.34 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There are no known cases of overdose with KISQALI. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

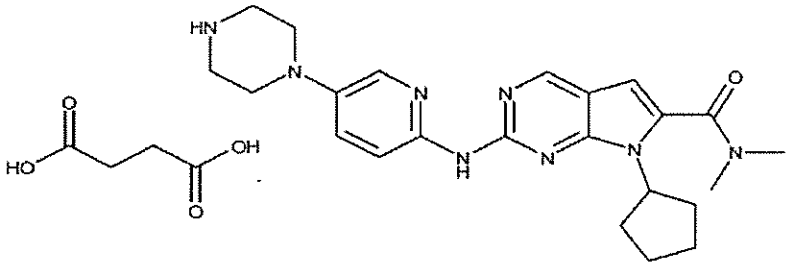
11 DESCRIPTION

KISQALI (ribociclib) is a kinase inhibitor.

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).

Ribociclib succinate is a light yellow to yellowish brown crystalline powder. 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/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 hydrolysed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

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. In 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

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)]*.

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).

Absorption

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

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).

Distribution

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 (Vss/F) was 1090 L based on population PK analysis.

Metabolism

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).

Elimination

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 (T1/2) 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.

Specific Populations

Patients with Hepatic Impairment

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_{max}; 1.32 for AUC_{inf}) and severe (Child-Pugh class C; GMR: 1.34 for C_{max}; 1.29 for AUC_{inf}) 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.

Patients with Renal Impairment

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

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_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. 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 C_{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_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by

27%, respectively. A moderate CYP3A inducer (efavirenz) is predicted to decrease ribociclib C_{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_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. Administration of ribociclib at 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 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 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

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 ≥75 mg/kg in rats and ≥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.

13.2 Animal Toxicology and/or Pharmacology

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

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 plus letrozole (n= 334) or placebo plus 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.

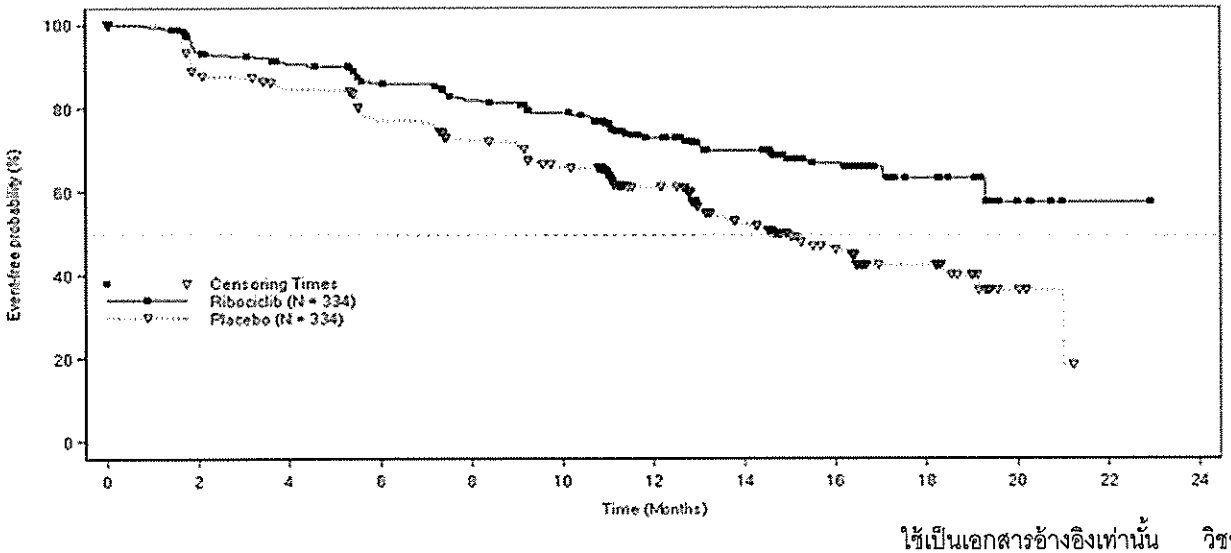
The efficacy results from Study 1 are summarized in Table 8 and Figure 1. The results shown are from a pre-planned interim efficacy analysis of PFS. Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and 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)

	KISQALI + letrozole	**Placebo + letrozole**
Progression-free survival	**N = 334**	**N = 334**
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[a]	
Overall Response Rate	**N=256**	**N=245**
Patients with measurable disease (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)

[a]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 (ribociclib) Tablets

Each film-coated tablet contains 200 mg of ribociclib free base.

Light greyish violet, round, curved with beveled edge, debossed with "RIC" on one side and "NVR" on the other side; available in:

Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (600 mg daily dose)
Outer container - 3 Blister packs per outer container NDC 0078-0874-63

Blister pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (400 mg daily dose)
Outer container - 3 Blisters packs per outer container NDC 0078-0867-42

Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (200 mg daily dose)
Outer container – 1 Blister pack per outer container NDC 0078-0860-01

Store 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).

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 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 *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise lactating women not to breastfeed during treatment with KISQALI 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 *[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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