Liver-related events with KISQALI

Managing potential side effects in HR+/HER2- early (stage II/III at high risk of recurrence) and metastatic breast cancer

HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Indications

KISQALI is indicated:

- in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer (eBC) at high risk of recurrence
- for the treatment of adults with HR-positive, HER2-negative advanced or metastatic breast cancer (mBC) in combination with:
  - an aromatase inhibitor as initial endocrine-based therapy; or
  - fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy

IMPORTANT SAFETY INFORMATION

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

In patients with eBC (NATALEE) who received 400 mg KISQALI plus a nonsteroidal aromatase inhibitor (NSAI), 1.5% of patients had ILD/pneumonitis (grade 1/2).

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of patients had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

With 33.3 months of follow-up, in the adjuvant setting, for patients with stage II/III HR+/HER2- eBC,

No new safety signals were observed with KISQALI

ADVERSE REACTIONS (≥10% AND ≥2% HIGHER THAN AI-ALONE ARM) IN NATALEE[1]

	KISQALI + AI (n=2526)		AI alone (n=2441)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
INFECTIONS AND INFESTATIONS				
Infections*	37	2	27	0.9
NERVOUS SYSTEM DISORDERS				
Headache	23	0.4†	17	0.2†
GASTROINTESTINAL DISORDERS				
Nausea	23	0.2†	8	0.1†
Diarrhea	15	0.6†	6	0.1†
Constipation	13	0.2†	5	0
Abdominal pain	11	0.5†	7	0.4†
GENERAL DISORDERS AND ADMINISTRATION-SITE CONDITIONS				
Fatigue	22	0.8†	13	0.2†
Asthenia	17	0.6†	12	0.1†
Pyrexia	11	0.2†	6	0.1†
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Alopecia	15	0	4.6	0
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Cough	13	0.1†	8	0.1†

AI, aromatase inhibitor; ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; eBC, early breast cancer.

The NATALEE trial was designed to maximize the efficacy benefit of KISQALI while minimizing dose-dependent ARs and adherence issues related to tolerability[2]

- The most common ARs (occurring in ≥20% of patients treated with KISQALI), including laboratory abnormalities, were decrease in lymphocytes, decrease in leukocytes, decrease in neutrophils, decrease in hemoglobin, increase in ALT, increase in AST, infections, increase in creatinine, decrease in platelets, headache, nausea, and fatigue[1]
- The most common grade ≥3 ARs, including laboratory abnormalities, occurring in ≥5% of patients were decrease in neutrophils, decrease in leukocytes, decrease in lymphocytes, increase in ALT, and increase in AST[1]
- Fatal ARs occurred in 0.6% of patients who received KISQALI. Fatal ARs in ≥0.1% of patients receiving KISQALI included COVID-19 or COVID-19 pneumonia (0.2%) and pulmonary embolism (0.1%)[1]

Grading according to CTCAE version 4.03.
*Infections included urinary and respiratory tract infections.
†Only includes grade 3 ARs.

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With 33.3 months of follow-up, in the adjuvant setting, for patients with stage II/III HR+/HER2- eBC,

No new lab abnormalities were observed with KISQALI

SELECT LABORATORY ABNORMALITIES (≥10%) IN NATALEE[1]

	KISQALI + AI (n=2526)		AI alone (n=2441)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
HEMATOLOGY				
Lymphocyte count decreased	97	19	88	6
Leukocyte count decreased	95	27	45	0.6
Neutrophil count decreased	94	45	35	1.7
Hemoglobin decreased	47	0.6	26	0.3
Platelet count decreased	28	0.4	13	0.3
CHEMISTRY				
ALT increased	45	8	35	1
AST increased	44	5	33	1
Creatinine increased	33	0.3	11	0

- Grade 4 increases in ALT (1.5%) and AST (0.8%) were reported in the KISQALI + AI arm[1]
- Drug-induced liver injury was reported in 9 patients (0.4%), of which 5 were grade ≥3, and 8 had resolved as of the data cutoff. There were 8 (0.3%) clinically confirmed Hy's Law cases (including 4 out of 9 drug-induced liver injury mentioned above), 6 of which had resolved within 303 days and 2 of which were improving, all after discontinuation of KISQALI[1]

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

In HR+/HER2- eBC,

Liver-related safety data in patients receiving KISQALI + AI

CLINICAL TRIAL DATA[1,3]

	Laboratory abnormalities* (all grades)	Adverse events† (all grades)	Grade 3/4 laboratory abnormalities*
NATALEE: KISQALI + AI			
ALT increased	45%	19.5%	8%
AST increased	44%	16.9%	5%

- In NATALEE, any-grade ALT and AST increased (AEs) occurred in 5.6% and 5.7% of patients in the NSAI + placebo arm, respectively[3,†]
- Grade ≥3 liver-related AEs (ALT or AST increased)[3]
  - Median time to onset: **2.9 months**
  - Median time to resolution (to grade ≤2): **0.7 months**

Dose modifications and discontinuations due to liver-related AEs in the KISQALI + AI arm of NATALEE[1]:

- Discontinuation due to ALT or AST increased: 8%
- Dose interruption due to ALT or AST increased: 11%
- Dose reductions due to liver function abnormalities: 2.3%

*Laboratory abnormalities in the US Prescribing Information for KISQALI.

†Adverse events from the NATALEE trial final analysis. Defined as inducing signs or symptoms requiring therapeutic intervention or requiring changes in trial treatment. All-grade and grade 3/4 events were defined using CTCAE version 4.03.

In HR+/HER2- eBC, grade 3/4 ALT or AST increase was observed in 8% and 5% of patients, respectively

AE, adverse event; NSAI, nonsteroidal aromatase inhibitor.

IMPORTANT SAFETY INFORMATION (continued)

Interstitial lung disease/pneumonitis (continued). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis.

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

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Safety from the MONALEESA clinical trials

Select adverse reactions (ARs) in <10% of patients who received KISQALI + ET[1]

Interstitial lung disease/pneumonitis:

- 1.6% of patients had ILD/pneumonitis (any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome)
- Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea

SCARs:

- Cases of SJS, TEN, and DiHS/DRESS have been reported. If signs or symptoms of severe cutaneous reactions occur, interrupt KISQALI until the etiology of the reaction has been determined. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management. If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI

QT prolongation:

- **Avoid KISQALI in patients who are at significant risk of developing torsades de pointes, including those with:**
  - congenital long QT syndrome
  - uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism
  - electrolyte abnormalities
  - taking drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval
- In patients with HR+/HER2- mBC who received KISQALI + AI or fulvestrant
  - 1.4% had a >500 ms postbaseline QTcF value
  - 6% had a >60 ms QTcF increase from baseline
  - There were no reported cases of torsades de pointes
- QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI
- In MONALEESA-2, in the KISQALI plus letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3

QT prolongation increased with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen.

Embryo-fetal toxicity:

- KISQALI can cause fetal harm when administered to a pregnant woman. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose

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In the MONALEESA-2 trial, fatal ARs occurred in 1.8% of patients who received KISQALI. Fatal ARs in ≥0.1% of patients receiving KISQALI included acute respiratory failure (0.6%), acute myocardial infarction, sudden death (with grade 3 hypokalemia and grade 2 QT prolongation), unknown cause, and pneumonia (0.3% each). In the MONALEESA-3 trial, fatal ARs occurred in 1.2% of patients who received KISQALI. Fatal ARs in ≥0.1% of patients receiving KISQALI included cardiac failure, ventricular arrhythmia, pneumonia, acute respiratory distress, pulmonary embolism, and hemorrhagic shock (0.2% each).

Please see Prescribing Information for a full list of adverse reactions.

CYP3A, cytochrome P450, family 3, subfamily A; DiHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; ET, endocrine therapy; ILD, interstitial lung disease; mBC, metastatic breast cancer; QTcF, QT interval corrected by Fridericia's formula; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

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Select ARs in ≥10% of patients who received KISQALI + ET

LABORATORY ABNORMALITIES IN ≥10% OF PATIENTS WHO RECEIVED KISQALI + ET[1]

	MONALEESA-2				MONALEESA-3				MONALEESA-7			
	KISQALI + letrozole (n=334)		Placebo + letrozole (n=330)		KISQALI + fulvestrant (n=483)		Placebo + fulvestrant (n=241)		KISQALI + NSAI + goserelin (n=248)		Placebo + NSAI + goserelin (n=247)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Neutrophil count decreased	93	60	24	1.2	92	53	21	0.8	92	63	27	2.4
ALT increased	46	10	36	1.2	44	11	37	1.7	33	6	31	1.6
AST increased	44	7	32	1.5	50	7	43	2.9	37	4.8	35	1.6

Hepatotoxicity:
Across the 3 trials, the median time to onset of grade ≥3 ALT/AST elevation was 92 days for the KISQALI + AI or fulvestrant treatment arms. The median time to resolution to grade ≤2 was 21 days in the KISQALI + AI or fulvestrant treatment arms. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 6 (1%) patients, and all patients recovered after discontinuation of KISQALI. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation.[1]

Neutropenia:
KISQALI causes concentration-dependent neutropenia. Across the 3 trials, the median time to grade ≥2 neutropenia was 17 days. The median time to resolution of grade ≥3 neutropenia to grade <3 was 12 days. Treatment discontinuation due to neutropenia was required in 1% of patients. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.[1]

ULN, upper limit of normal.

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Dose modifications due to ARs

DOSE MODIFICATIONS DUE TO ARs WITH KISQALI + AI OR FULVESTRANT[1]

	MONALEESA-2	MONALEESA-3	MONALEESA-7
	KISQALI + letrozole (n=334)	KISQALI + fulvestrant (n=483)	KISQALI + NSAI + goserelin (n=248)
Dose interruption due to ARs	71%	72%	73%
Dose reduction due to ARs	45%	32%	33%
Permanent discontinuation due to ARs	7%	8%	3%

In a pooled analysis of the MONALEESA-2, -3, and -7 trials, the most common (≥20%) ARs, including laboratory abnormalities, were leukocytes decreased (95%), neutrophils decreased (93%), hemoglobin decreased (68%), lymphocytes decreased (66%), AST increased (55%), gamma-glutamyl transferase increased (53%), ALT increased (52%), infections (47%), nausea (47%), creatinine increased (42%), fatigue (35%), platelets decreased (34%), diarrhea (33%), vomiting (29%), headache (27%), constipation (25%), alopecia (25%), cough (24%), rash (24%), back pain (24%), and glucose serum decreased (20%).[1]

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

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In HR+/HER2- mBC,

Liver-related safety data in patients receiving KISQALI + ET

CLINICAL TRIAL DATA [1,4-6]

	Laboratory abnormalities* (all grades)	Adverse events† (all grades)	Grade 3/4 laboratory abnormalities*
MONALEESA-2: KISQALI + AI[1,4]			
ALT increased	46%	15.6%	10%
AST increased	44%	15%	7%
MONALEESA-3: KISQALI + FULVESTRANT[1,5]			
ALT increased	44%	14.5%	11%
AST increased	50%	13.3%	7%
MONALEESA-7: KISQALI + NSAI + GOSERELIN[1,6]			
ALT increased	33%	17.7%	6%
AST increased	37%	17.7%	4.8%

DISCONTINUATIONS DUE TO LIVER-RELATED AEs ACROSS TRIALS[1]

	MONALEESA-2	MONALEESA-3	MONALEESA-7
	KISQALI + letrozole (n=334)	KISQALI + fulvestrant (n=483)	KISQALI + NSAI + goserelin (n=248)
Discontinuations due to ALT elevations	5%	5%	2%
Discontinuations due to AST elevations	3%	3%	2%

- In MONALEESA-2, any-grade ALT and AST increased (AEs) occurred in 3.9% and 3.6% of patients in the NSAI + placebo arm, respectively[4,†]
- In MONALEESA-3, any-grade ALT and AST increased (AEs) occurred in 4.6% and 4.6% of patients in the fulvestrant + placebo arm, respectively[5,†]
- In MONALEESA-7, any-grade ALT and AST increased (AEs) occurred in 11.7 % and 11.3% of patients in the NSAI + placebo arm, respectively[6,†]
- Grade ≥3 ALT/AST elevation[1]
  - Median time to onset: **~3 months**
  - Median time to resolution (to grade ≤2): **0.7 months**
- In MONALEESA-2, dose reductions and interruptions due to ALT elevations (AEs) occurred in 3% and 5% of patients in the KISQALI arm, respectively[1]
- In MONALEESA-3, ALT and AST elevations (AEs) each led to dose interruptions in 8% of patients in the KISQALI arm[1]
- In MONALEESA-7, dose reductions due to ALT elevations (AEs) occurred in 2% of patients in the KISQALI arm[1]

*Laboratory abnormalities in the US Prescribing Information for KISQALI.

†Adverse-events rates as reported in the safety analysis of MONALEESA-2, -3, and -7 trials. Defined as inducing signs or symptoms requiring therapeutic intervention or requiring changes in trial treatment. All-grade and grade 3/4 events were defined using CTCAE version 4.03.

In HR+/HER2- mBC, grade 3/4 ALT/AST elevations were observed in ≤11% of patients in the KISQALI + AI or fulvestrant arms

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

In HR+/HER2- mBC,

Real-world, liver-related safety data in patients receiving KISQALI + ET

REAL-WORLD DATA[7]

	All-grade adverse events	Grade ≥3 adverse events
CompLEEment-1		
ALT increased	16.2%	7.7%
AST increased	14.1%	5.7%

CompLEEment-1 was a prospective study of 3246 patients with HR+/HER2- mBC who were treated with 1L KISQALI + AI between 2016 and 2018. The study included ECOG performance status 2, which was not included in the MONALEESA trials.[7]

Randomized, controlled clinical trials set the highest standard for data collection and for determining causation between variables. Real-world observational analyses are intended for supplemental use and are designed only to evaluate associations among variables. Real-world analyses cannot establish causality between treatments and outcomes and cannot control for systematic biases, and therefore should be interpreted with caution.

Due to lack of randomization and control arm, results from the CompLEEment-1 study should be interpreted with caution.

1L, first line; ECOG, Eastern Cooperative Oncology Group.

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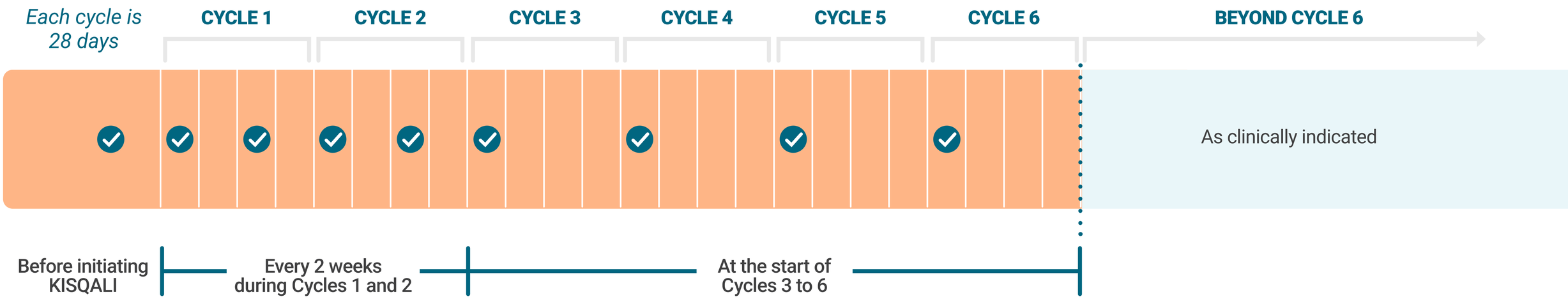
In HR+/HER2- eBC and mBC,

LFT monitoring and management

LFT monitoring[1]

Complete the following 6-cycle assessment schedule:



If grade ≥2 abnormalities are noted, monitor more frequently, and as clinically indicated.[1]

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation.[1]
Please refer to the Prescribing Information for KISQALI for full guidance on monitoring and dose modification.

LFT, liver function test.

IMPORTANT SAFETY INFORMATION (continued)

Severe cutaneous adverse reactions (continued). If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.
If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

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In HR+/HER2- eBC and mBC,

LFT monitoring and management (continued)

LIVER-RELATED AE MANAGEMENT[1]

	Grade 1 (> ULN to 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	**If grade 2 at baseline,*** no dose interruption	Dose interruption until recovery to ≤ baseline* grade, then resume at next lower dose level	Discontinue KISQALI
		If grade <2 at baseline, dose interruption until recovery to ≤ baseline* grade, then resume KISQALI at same dose level	**If grade 3 toxicity recurs,** discontinue KISQALI	
		If grade 2 toxicity recurs, reduce dose by 200 mg		
Discontinue KISQALI if patients develop ALT and/or AST >3 x ULN with total bilirubin >2 x ULN, regardless of baseline* grade				

Grading according to CTCAE version 4.03.
*Baseline=prior to treatment initiation.

Hepatic impairment[1]

- No dose adjustment is necessary in patients with breast cancer who have mild hepatic impairment (Child-Pugh class A)
- A reduced starting dose of 400 mg is recommended in patients with advanced or metastatic breast cancer who have moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C)

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.

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

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

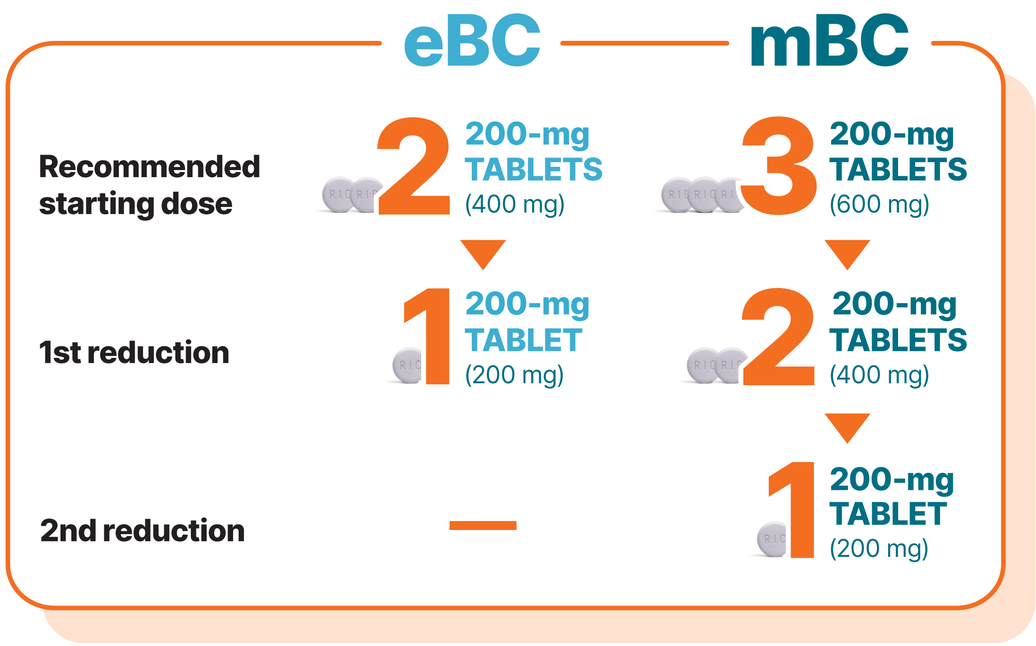
Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

In HR+/HER2- eBC and mBC,

KISQALI single-strength tablets make dose reduction simple and convenient

Dose reductions with KISQALI mean no need for new mid-cycle prescriptions or additional costs[1]



- Patients with mBC should continue treatment until disease progression or unacceptable toxicity[1]
- Patients with eBC should continue treatment for 3 years or until disease recurrence or unacceptable toxicity[1]
- Dose adjustments for ARs should be made stepwise by reducing the number of tablets taken[1]
- Dose modification is recommended based on individual safety and tolerability[1]
- If dose reduction below 200 mg/day is required, discontinue treatment[1]
- KISQALI can be taken with or without food[1]
- Store at room temperature at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)[1]
- Store in the original blister package in order to protect from moisture[1]

- KISQALI is given as 400 mg (2 x 200-mg tablets) and 600 mg (3 x 200-mg tablets) orally, once daily (3 weeks on, 1 week off) for HR+/HER2- eBC and HR+/HER2- mBC, respectively, with either[1]:
  - An AI once daily (continuously); in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines[1]; or
  - In mBC only: fulvestrant 500 mg intramuscularly on Days 1, 15, and 29, and once monthly thereafter; in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines[1]

LHRH, luteinizing hormone-releasing hormone.

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation (continued). Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

In patients with eBC (NATALEE) who received 400 mg KISQALI plus NSAI, 8 out of 2494 patients (0.3%) had > 500 ms post-baseline QTcF interval value and 50 out of 2494 patients (2%) had > 60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

MORE reasons to believe

KISQALI + AI is proven to treat both early (stage II and III at high risk of recurrence) and metastatic HR+/HER2- breast cancer—giving you more reasons to believe

NCCN CATEGORY 1

National Comprehensive Cancer Network® (NCCN®) **differentiates ribociclib (KISQALI®) as the first and only Category 1 Preferred treatment option when used in combination with an AI** for appropriate patients with HR+/HER2- mBC in 1L and for appropriate patients with HR+/HER2- eBC, including those with high-risk node-negative disease.[8]

In HR+/HER2- eBC, high-risk node-negative disease is defined as either tumor size >5 cm, or if tumor size 2-5 cm, either grade 2 (with high genomic risk Ki-67 ≥20%), or grade 3.[1,8]

There is controversy on the choice of CDK4/6i as there are no head-to-head comparisons between the agents and there are some differences in the study populations in the phase III randomized studies.[8]

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.[8]

#1 PRESCRIBED

KISQALI is the most prescribed CDK4/6 inhibitor in HR+/HER2- breast cancer[9]

September 2025 IQVIA custom breast cancer market sizing report.

NATALEE was a randomized, multicenter, open-label, phase III study of KISQALI + letrozole or anastrozole (n=2549) vs letrozole or anastrozole (n=2552) for the adjuvant treatment of men and women with stage II/III HR+/HER2- eBC. At a median follow-up of 33.3 months, with 509 events in the study (226 [8.9%] in the KISQALI arm and 283 [11.1%] in the NSAI-alone arm), iDFS (primary end point) at the 3-year landmark was 90.7% for KISQALI + NSAI vs 87.6% for NSAI alone **(absolute difference 3.1%)**; there was a 25.1% relative reduction in the risk of an iDFS event; HR=0.749 (95% CI: 0.628-0.892).[1,3,10]

MONALEESA-2 was a randomized, double-blind, placebo-controlled, phase III study of KISQALI + letrozole (n=334) vs placebo + letrozole (n=334) in postmenopausal patients with HR+/HER2- mBC who received no prior therapy for advanced disease. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 80 months, mOS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with placebo + letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004.[1,4,11]

CDK, cyclin-dependent kinase; HR, hazard ratio; iDFS, invasive disease-free survival; mOS, median overall survival; OS, overall survival; PFS, progression-free survival.

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation (continued). In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, and MONALEESA-7) who received 600 mg KISQALI plus NSAI or fulvestrant, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes. In MONALEESA-2, in the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

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References

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Indications

KISQALI is indicated:

- in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer (eBC) at high risk of recurrence
- for the treatment of adults with HR-positive, HER2-negative advanced or metastatic breast cancer (mBC) in combination with:
  - an aromatase inhibitor as initial endocrine-based therapy; or
  - fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy

IMPORTANT SAFETY INFORMATION

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

In patients with eBC (NATALEE) who received 400 mg KISQALI plus a nonsteroidal aromatase inhibitor (NSAI), 1.5% of patients had ILD/pneumonitis (grade 1/2).

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of patients had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis.

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

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

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

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.

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

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

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

In patients with eBC (NATALEE) who received 400 mg KISQALI plus NSAI, 8 out of 2494 patients (0.3%) had > 500 ms post-baseline QTcF interval value and 50 out of 2494 patients (2%) had > 60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, and MONALEESA-7) who received 600 mg KISQALI plus NSAI or fulvestrant, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes. In MONALEESA-2, in the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Perform electrocardiogram (ECG) in all patients prior to starting KISQALI. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorus and magnesium) prior to the initiation of KISQALI, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI.

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IMPORTANT SAFETY INFORMATION (continued)

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. Avoid use of tamoxifen with KISQALI. In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen + placebo subgroup compared with the nonsteroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Hepatotoxicity. In patients with eBC and advanced or mBC, drug-induced liver injury and increases in transaminases occurred with KISQALI.

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

In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) treated with KISQALI, grade 3 or 4 increases in ALT and AST occurred in 11% and 8%, respectively. Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. The median time to resolution to grade ≤2 was 21 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST >3x ULN and total bilirubin >2x ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) before initiating KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation.

Neutropenia. KISQALI causes concentration-dependent neutropenia. In patients with eBC (NATALEE) who received KISQALI plus NSAI, 94%, including 45% of grade 3/4, had a decrease in neutrophil counts (based on laboratory findings), 63% had an adverse drug reaction of neutropenia, and 0.3% had febrile neutropenia. The median time to grade ≥2 neutropenia was 18 days. The median time to resolution of grade ≥3 neutropenia to grade <3 was 10 days. Treatment discontinuation due to neutropenia was required in 1.1% of patients.

In patients with advanced or metastatic breast cancer (MONALEESA-2, MONALEESA-7, and MONALEESA-3) who received KISQALI plus NSAI or fulvestrant, 75% had neutropenia, 62% had grade 3/4 decrease in neutrophil count (based on laboratory findings), and 1.7% had febrile neutropenia. The median time to grade ≥2 neutropenia was 17 days. The median time to resolution of grade ≥3 neutropenia to grade <3 was 12 days. Treatment discontinuation due to neutropenia was required in 1% of patients.

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 of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

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. 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.

Adverse reactions in early breast cancer patients. Most common (incidence ≥20%) adverse reactions include infections, nausea, headache, and fatigue.

Laboratory abnormalities. In a clinical trial of patients with early breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were lymphocytes decreased, leukocyte decreased, neutrophil decreased, hemoglobin decreased, alanine aminotransferase increased, aspartate aminotransferase increased, creatinine increased, and platelets decreased**.

Adverse reactions in advanced or metastatic breast cancer patients. Most common (incidence ≥20%) adverse reactions include infections, nausea, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, and back pain.

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased**.

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