KISQALI®▼ (ribociclib)

THERAPY MANAGEMENT GUIDE

Optimising treatment for your patients

KISQALI in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy.[1]

HR+/HER- = Hormone-receptor-positive and human epidermal growth factor receptor 2-negative.

Prescribing Information can be found on pages 22 and 23 of this document.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis Pharmaceuticals UK Ltd on 01276 698370, at medinfo.uk@novartis.com or online through the patient safety information tool at https://psi.novartis.com

▼ This medicinal product is subject to additional monitoring.

KISQALI® ribociclib

KISQALI is a CDK4/6 inhibitor for first-line HR+/HER2- locally advanced or metastatic breast cancer treatment.[1]

This guide provides information for healthcare professionals about how to use KISQALI, detailing posology, how to monitor patients, and how to manage important adverse events.

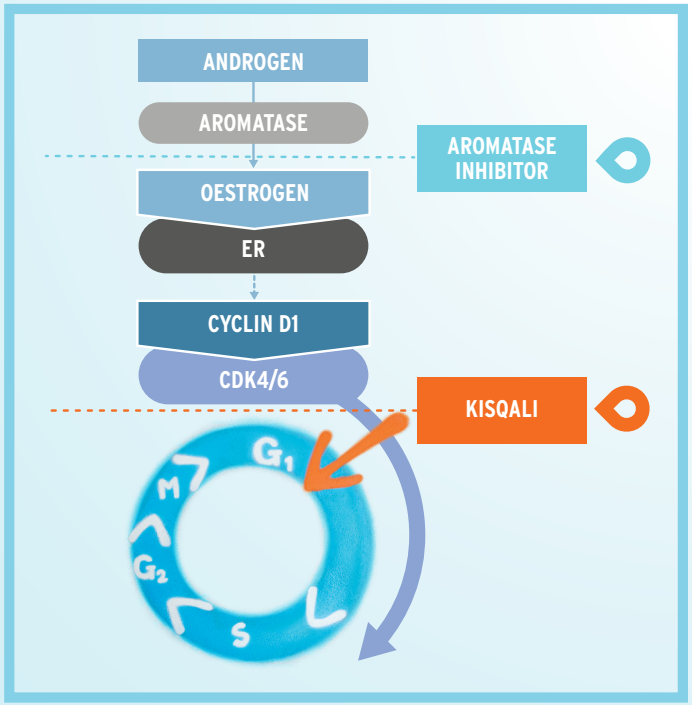
INDICATION[1]

KISQALI in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy.

MECHANISM OF ACTION[1]

KISQALI is a selective inhibitor of CDK4/6, which play a crucial role in signalling pathways that lead to cell cycle progression and cellular proliferation.

KISQALI works with an aromatase inhibitor (e.g. letrozole) to induce G_1 arrest and delay disease progression.[1]



CDK4/6 = cyclin-dependent kinases 4 and 6; ER = oestrogen receptor; G_1 = gap phase 1.

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PHARMACEUTICAL FORM[1]

KISQALI is available as 200 mg film-coated tablets.

Diameter: 11.1 mm.

STARTING DOSE[1]

The recommended starting dose is **600 mg/day** (3 x 200 mg tablets).

- A reduced starting dose may be required for special populations.

RECOMMENDED STARTING DOSES OF KISQALI FOR SPECIAL POPULATIONS[1]

RENAL IMPAIRMENT	
MILD (eGFR 60 to <90 ml/min/1.73 m²)	No dose adjustment required.
MODERATE (eGFR 30 to <60 ml/min/1.73 m²)	No dose adjustment required.
SEVERE (eGFR <30 ml/min/1.73 m²)	Caution should be used in patients with severe renal impairment with close monitoring of signs of toxicity as there is no experience with KISQALI in this population.
HEPATIC IMPAIRMENT	
MILD (Child-Pugh class A)	No dose adjustment required.
MODERATE (Child-Pugh class B)	The recommended starting dose is 400 mg/day.
SEVERE (Child-Pugh class C)	The recommended starting dose is 400 mg/day.
PAEDIATRIC AND ELDERLY POPULATIONS	
PAEDIATRIC POPULATION (aged <18 years)	The safety and efficacy of KISQALI in children and adolescents aged below 18 years have not been established as no data are available.
ELDERLY (aged >65 years)	No dose adjustment required.

The use of KISQALI should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. These include patients with the following:

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

A reduced dose of KISQALI may be required when strong CYP3A4 inhibitors are concomitantly administered.

Dose adjustments with strong CYP3A4 inhibitors are detailed on page 19 of this guide.

eGFR = estimated glomerular filtration rate; QTc = Corrected QT interval.

DOSING SCHEDULE[1]

KISQALI should be taken as part of a 28-day treatment cycle comprising a once-daily dose of KISQALI for 21 consecutive days followed by 7 consecutive days off treatment. Treatment with KISQALI should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

KISQALI should be used together with 2.5 mg letrozole or another aromatase inhibitor. The aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Summary of Product Characteristics of the aromatase inhibitor for additional details.

RECOMMENDED DOSING SCHEDULE FOR KISQALI (28-DAY CYCLE)[1]

	WEEK 1	WEEK 2	WEEK 3	WEEK 4
KISQALI  600 mg (3 x 200 mg tablets) once daily for 21 consecutive days followed by 7 days off treatment.	✓	✓	✓	
AROMATASE INHIBITOR (e.g. 2.5 mg letrozole) Once daily continuously throughout the 28-day cycle. Please see the Summary of Product Characteristics for the aromatase inhibitor for details.	✓	✓	✓	✓

Patients should take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking a dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

METHOD OF ADMINISTRATION[1]

KISQALI should be taken orally once daily with or without food. KISQALI tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing. No tablet should be ingested if it is broken, cracked or otherwise not intact.

KISQALI can be administered with or without food, but patients should be instructed to avoid pomegranates, pomegranate juice, grapefruit and grapefruit juice. These are known to inhibit CYP3A4 enzymes and may increase the exposure to Kisqali.[1]

DOSE MODIFICATIONS

Management of severe or intolerable adverse events may require temporary dose interruption, reduction or discontinuation of KISQALI.[1]

RECOMMENDED STEPWISE DOSE MODIFICATIONS[1]

RECOMMENDED STARTING DOSE	FIRST DOSE REDUCTION	SECOND DOSE REDUCTION
600 mg/day (3 x 200 mg tablets)	**400 mg/day** (2 x 200 mg tablets)	**200 mg/day** (1 x 200 mg tablet)

If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.

Dose modifications for specific adverse events are detailed on pages 10–17 of this guide.

MONITORING

It is recommended that certain blood tests and an ECG assessment be performed prior to and during treatment with KISQALI.[1]

RECOMMENDED MONITORING SCHEDULE[1]

		CYCLE 1	CYCLE 2	CYCLES 3–6	THEREAFTER
BLOOD					
FBC LFTs	Test prior to initiation.	Day 14	Days 1 and 14	Day 1 of each cycle	As clinically indicated
Electrolytes	Test prior to initiation. Correct any abnormalities before initiating treatment with KISQALI.	Day 1	Day 1	Day 1 of each cycle	As clinically indicated
CARDIAC					
ECG	Test prior to initiation. KISQALI should only be initiated in patients with QTcF <450 msec.	Day 14	Day 1	As clinically indicated	As clinically indicated

- **More frequent monitoring is recommended in the event of liver enzyme elevations at grade ≥2 or QTcF prolongation during treatment.**

As a result of monitoring, adverse events which require dose modification may be identified. Dose modifications for specific adverse events are detailed on pages 10–17 of this guide.

ECG = electrocardiogram; FBC = full blood count; LFT = liver function test; QTcF = QT interval corrected using Fridericia's formula.

Adverse events profile

Frequencies of adverse events with KISQALI reported in MONALEESA-2, a Phase III clinical study, are listed below. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); and very rare (<1/10,000).[1]

FREQUENCIES OF ADVERSE EVENTS OBSERVED WITH KISQALI IN MONALEESA-2[1]

AE	FREQUENCY
Infections and infestations	
Urinary tract infection	Very common
Blood and lymphatic system disorders	
Neutropenia	Very common
Leukopenia	Very common
Anaemia	Very common
Lymphopenia	Very common
Thrombocytopenia	Common
Febrile neutropenia	Common
Metabolism and nutrition disorders	
Decreased appetite	Very common
Hypocalcaemia	Common
Hypokalaemia	Common
Hypophosphataemia	Common
Nervous system disorders	
Headache	Very common
Insomnia	Very common
Eye disorders	
Lacrimation increased	Common
Dry eye	Common
Cardiac disorders	
Syncope	Common
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	Very common
Epistaxis	Common

AE	FREQUENCY
Gastrointestinal disorders	
Nausea	Very common
Diarrhoea	Very common
Vomiting	Very common
Constipation	Very common
Stomatitis	Very common
Abdominal pain	Very common
Dysgeusia	Common
Dyspepsia	Common
Hepatobiliary disorders	
Hepatotoxicity*	Common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Rash†	Very common
Pruritus	Very common
Erythema	Common
Musculoskeletal and connective tissue disorders	
Back pain	Very common
General disorders and administration site conditions	
Fatigue	Very common
Peripheral oedema	Very common
Asthenia	Very common
Pyrexia	Very common
Investigations	
Abnormal liver function tests‡	Very common
Blood creatinine increased	Common
Weight decreased	Common
Electrocardiogram QT prolonged	Common

For a full list of adverse events, please consult the Summary of Product Characteristics for KISQALI.

*Hepatotoxicity: hepatocellular injury, drug induced liver injury, hepatotoxicity, hepatic failure (single non-fatal case), autoimmune hepatitis (single case).

†Rash: rash, rash maculopapular.

‡Abnormal liver function tests: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased.

AE = adverse event

CLINICAL INCIDENCE[1]

Neutropenia is a very common adverse event associated with KISQALI treatment (occurring at a frequency of ≥1/10 patients), and was the most frequently reported adverse event in MONALEESA-2.

NEUTROPENIA* EVENTS REPORTED IN PATIENTS RECEIVING KISQALI (N=334) IN MONALEESA-2[1]

EVENT†	PROPORTION OF PATIENTS WITH AT LEAST ONE EVENT (%)
Neutropenia at any grade	74.3
Neutropenia at grade 3 or 4	59.6
Febrile neutropenia	1.5

TIME TO ONSET AND IMPROVEMENT OF NEUTROPENIA IN MONALEESA-2[1]

16 days

Among the patients who had grade 2, 3 or 4† neutropenia, the median time to onset was **16 days**.

The median time to improvement of grade ≥3† events with KISQALI (to grade <3) was **15 days** following treatment interruption and/or reduction and/or discontinuation.

15 days

*Decrease in neutrophil count, based on laboratory findings.

†Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03[2]: grade 3 neutropenia: ANC 500 to 1000/mm³; grade 4 neutropenia: ANC <500/mm³.

ANC = absolute neutrophil count.

NEUTROPENIA MANAGEMENT ALGORITHM[1]

Full blood counts should be performed before initiating with KISQALI. After initiation of KISQALI, full blood count should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.

Clinical description	ANC 1000/mm³ to ≤LLN (Grades 1 or 2*)	ANC 500–1000/mm³ (Grade 3*)	Grade 3* neutropenia with a single fever >38.3°C [or >38°C for more than 1 hour and/or concurrent infection] (Grade 3* febrile neutropenia)	ANC <500/mm³ (Grade 4*)
Dose modification	No dose adjustment is required.	Dose interruption until recovery to grade ≤2.	Dose interruption until recovery to grade ≤2.	Dose interruption until recovery to grade ≤2.
Follow-up		*If neutropenia improves to grade ≤2:* Resume KISQALI at the same dose level. *If toxicity recurs at grade 3:* Dose interruption until recovery to grade ≤2, then resume KISQALI and reduce by one dose level.	*If neutropenia improves to grade ≤2:* Resume KISQALI and reduce by one dose level.	*If neutropenia improves to grade ≤2:* Resume KISQALI and reduce by one dose level.

If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.

*Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.[2]

LLN = lower limit of normal.

CLINICAL INCIDENCE[1]

Hepatobiliary toxicity events* are a common adverse event associated with KISQALI treatment, (occurring at a frequency of ≥1/100 patients, but <1/10 patients). Abnormal liver function tests are a very common adverse event (occurring at a frequency of ≥1/10 patients).

HEPATOBILIARY TOXICITY EVENTS REPORTED IN PATIENTS RECEIVING KISQALI (N=334) IN MONALEESA-2[1]

EVENT†	PROPORTION OF PATIENTS WITH AT LEAST ONE EVENT (%)
Any hepatobiliary toxicity event	
At any grade	24.0
At grade 3 or 4	11.4
ALT elevations at grade 3 or 4	10.2
AST elevations at grade 3 or 4	6.9

Concurrent elevations in ALT or AST >3 x ULN and total bilirubin >2 x ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 (1.2%) patients receiving KISQALI in MONALEESA-2, all of whom recovered to normal levels within 154 days after treatment with KISQALI was discontinued.

TIME TO ONSET AND IMPROVEMENT OF LIVER ENZYME ELEVATIONS IN MONALEESA-2 AND A PHASE IB STUDY OF KISQALI PLUS LETROZOLE[1]

57 days

The majority (83.8%) of grade 3 or 4† ALT/AST elevation events occurred within the first 6 months of treatment. Among the patients who had grade 3 or 4† ALT/AST elevation, the median time to onset was **57 days**.

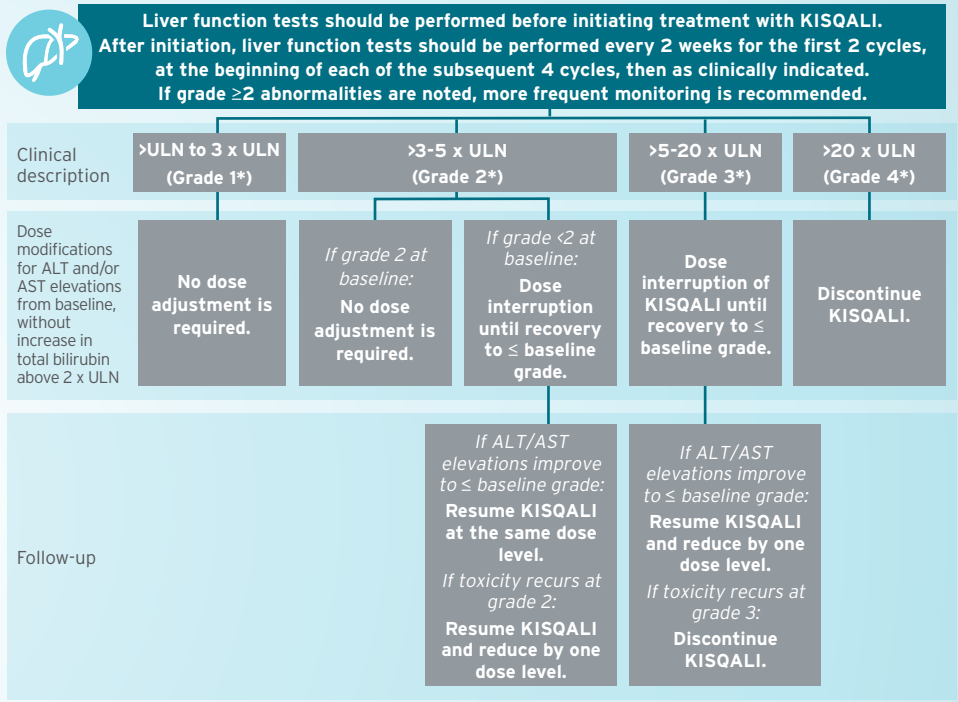
The median time to improvement (to grade ≤2) was **24 days**.

24 days

Based on the severity of the transaminase elevations, treatment with KISQALI may have to be interrupted, reduced or discontinued as described on the page opposite. In MONALEESA-2, discontinuation of KISQALI due to abnormal liver function tests or hepatotoxicity occurred in 3.0% and 0.6% of patients respectively.

Recommendations for patients who have grade ≥3 ALT/AST elevation at baseline have not been established.

ALT/AST MANAGEMENT ALGORITHM[1]



If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue KISQALI.

If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.

*Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.[2]

Page 12 footnotes:

*Hepatotoxicity included hepatocellular injury, drug-induced liver injury, hepatotoxicity, hepatic failure (of which there was a single non-fatal case) and autoimmune hepatitis (of which there was a single case).

†Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03[2]: grade 3 ALT/AST elevation: >5-20 x ULN; grade 3 ALT/AST elevation: >20 x ULN.

ULN = upper limit of normal.

CLINICAL INCIDENCE[1]

QT prolongation is a common adverse event associated with KISQALI treatment (occurring at a frequency of ≥1/100 patients, but fewer than 1/10 patients).

QT INTERVAL PROLONGATION REPORTED IN PATIENTS RECEIVING KISQALI (N=334) IN MONALEESA-2[1]

EVENT	PROPORTION OF PATIENTS WITH AT LEAST ONE EVENT (%)
Any QT interval prolongation (including ECG QT prolonged and syncope)	7.5
QTcF interval >500 msec	0.3
QTcF interval >480 msec	3.3
QTcF increase >60 msec from baseline	2.7

7.5% of patients had at least one event of QT interval prolongation (including ECG QT prolonged and syncope) with KISQALI. There were no reported cases of torsade de pointes. Dose interruptions/adjustments due to ECG QT prolongation and syncope were reported in 0.9% of patients who were receiving KISQALI.

TIME TO ONSET OF QT INTERVAL PROLONGATION IN MONALEESA-2[1,3]

4 weeks

QTcF interval prolongation >480 msec with KISQALI mostly occurred within the first **4 weeks** of treatment.

15 days

Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was **15 days**, and these changes were reversible with dose interruption and/or dose reduction.

Based on the severity of QT interval prolongation, treatment with KISQALI may have to be interrupted, reduced or discontinued as described on the page opposite.

QT PROLONGATION MANAGEMENT ALGORITHM[1]

ECG should be assessed before initiating treatment. Treatment with KISQALI should be initiated only in patients with QTcF values <450 msec. After initiation, ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

Clinical description	**ECGs with QTcF >480 msec**	**ECGs with QTcF >500 msec**
Dose modification	**Dose interruption until recovery to <481 msec**	*If QTcF is greater than 500 msec on at least two separate ECGs:* **Interrupt KISQALI until QTcF is <481 msec**
		*If QTcF interval prolongation to greater than 500 msec or greater than 60 msec change from baseline occurs **in combination with** torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia:* **Permanently discontinue KISQALI.**
Follow-up	*If QTcF improves to <481 msec:* **Resume KISQALI at the same dose level.** *If QTcF prolongation recurs at ≥481 msec:* **Dose interruption until QTcF improves to <481 msec and then resume KISQALI and reduce by one dose level.**	*If QTcF improves to <481 msec:* **Resume KISQALI and reduce by one dose level.**

If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.

CLINICAL INCIDENCE[1]

The most common adverse events of any grade (reported in ≥20% of patients) for which the frequency for KISQALI plus letrozole exceeds the frequency for placebo plus letrozole were:

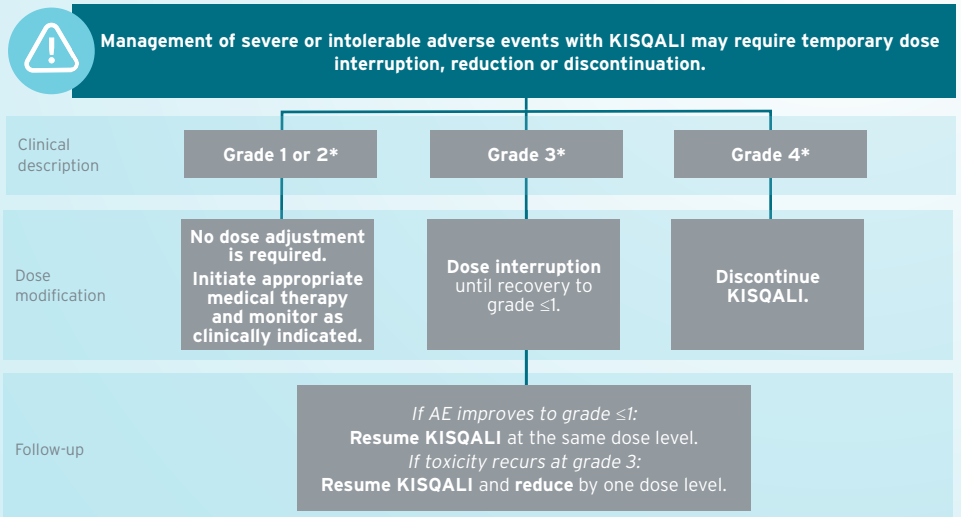
- neutropenia
- leukopenia
- headache
- back pain
- nausea
- fatigue
- diarrhoea
- vomiting
- constipation
- alopecia
- rash

The most common adverse events at grade 3 or 4 (reported in ≥2% of patients) for which the frequency for KISQALI plus letrozole exceeds the frequency for placebo plus letrozole were:

- neutropenia
- leukopenia
- abnormal liver function test
- lymphopenia
- hypophosphataemia
- vomiting
- nausea
- fatigue
- back pain

Management of severe or intolerable adverse events with KISQALI may require temporary dose interruption, reduction or discontinuation, as described on the page opposite.

GENERAL ADVERSE EVENTS MANAGEMENT ALGORITHM[1]



If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.

*Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.[2]

AE	GRADES 1 & 2	GRADE 3	GRADE 4
Vomiting	1–5 episodes separated by 5 minutes) in 24 hours	≥6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalisation indicated	Life-threatening consequences; urgent intervention indicated
Headache	Mild or moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	N/A
Back pain	Mild or moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	N/A
Fatigue	Fatigue relieved by rest, or fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	N/A
Nausea	Loss of appetite without alteration in eating habits, *or* oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalisation indicated	N/A
Diarrhoea	Increase of <7 stools per day over baseline; mild to moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema, *or* Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Alopecia	Any hair loss that is abnormal for that individual	N/A	N/A
Rash (maculopapular)	Macules/papules covering <30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	N/A
Hypophosphataemia	<LLN to 2.0 mg/dL; <LLN to 0.6 mmol/L	<2.0–1.0 mg/dL; <0.6–0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences
Leukopenia	<LLN to 2000/mm^3; <LLN to 2.0 x 10^9/L	<2000–1000/mm^3; <2.0–1.0 x 10^9/L	<1000/mm^3; <1.0 x 10^9/L
Lymphopenia	<LLN to 500/mm^3; <LLN to 0.5 x 10^9/L	<500–200/mm^3; <0.5–0.2 x 10^9/L	<200/mm^3; <0.2 x 10^9/L

Adapted from Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.2

ADL = activities of daily living; BSA = body surface area; LLN = lower limit of normal; N/A = grade is not available; TPN = total parenteral nutrition.

Other special warnings and precautions

EFFECTS DURING PREGNANCY AND LACTATION, AND ON FERTILITY

KISQALI is indicated for use in postmenopausal women, but please note the following effects of its active ingredient during pregnancy and lactation and on fertility.

Pregnancy status should be verified prior to starting treatment with KISQALI.

Based on findings in animals, KISQALI can cause foetal harm when administered to a pregnant woman.

CRITICAL VISCERAL DISEASE

The efficacy and safety of KISQALI have not been studied in patients with critical visceral disease.

SOYA LECITHIN

KISQALI contains soya lecithin. Patients who are hypersensitive to peanut or soya should not take KISQALI.

Interactions: effects on KISQALI by other products

KISQALI is primarily metabolised by CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of KISQALI.

STRONG CYP3A4 INHIBITORS[1]

The concomitant use of strong CYP3A4 inhibitors, including but not limited to the following, must be avoided:

- Clarithromycin
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir
- Ritonavir
- Nefazodone
- Nelfinavir
- Posaconazole
- Saquinavir
- Telaprevir
- Telithromycin
- Verapamil
- Voriconazole

Alternative concomitant medicinal products with less potential to inhibit CYP3A4 should be considered and patients should be monitored for adverse events.

- If co-administration of KISQALI with a strong CYP3A4 inhibitor cannot be avoided, the dose of KISQALI should be reduced to 400 mg; however, there are no clinical data with this dose adjustment.
- In patients who have had their dose reduced to 400 mg and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 200 mg. In patients who have had their dose reduced to 200 mg and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, KISQALI treatment should be interrupted.
- Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients; therefore, close monitoring for adverse events is recommended. In the event of toxicity related to KISQALI, the dose should be modified or treatment should be interrupted until toxicity is resolved. If the strong inhibitor is discontinued, the KISQALI dose should be resumed (after at least five half-lives of the CYP3A4 inhibitor) at the dose used prior to the initiation of the strong CYP3A4 inhibitor.
- **Patients should be instructed to avoid pomegranates, pomegranate juice, grapefruit and grapefruit juice.** These are known to inhibit CYP3A4 enzymes and may increase the exposure to KISQALI.

STRONG CYP3A4 INDUCERS[1]

The concomitant use of strong CYP3A4 inducers, including but not limited to the following, should be avoided:

- Phenytoin
- Rifampin
- Carbamazepine
- St John's wort (*Hypericum perforatum*)

Alternative concomitant medicinal products with no or minimal potential to induce CYP3A4 should be considered and patients should be monitored for adverse events.

For a full list of potential interactions, please consult the Summary of Product Characteristics for KISQALI.

Interactions: effects on other products by KISQALI

CYP3A4 SUBSTRATES[1]

KISQALI is a moderate to strong CYP3A4 inhibitor and may interact with medicinal substrates that are metabolised via CYP3A4, which can lead to increased serum concentrations of the concomitantly used medicinal product.

Caution is recommended when KISQALI is administered with sensitive CYP3A4 substrates with a narrow therapeutic index. The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index, including but not limited to the following, may need to be reduced as KISQALI can increase their exposure:

- Alfentanil
- Ciclosporin
- Everolimus
- Fentanyl
- Sirolimus
- Tacrolimus

Concomitant administration of KISQALI at the 600 mg dose with the following CYP3A4 substrates should be avoided:

- Alfuzosin
- Amiodarone
- Cisapride
- Pimozide
- Quinidine
- Ergotamine
- Dihydroergotamine
- Quetiapine
- Lovastatin
- Simvastatin
- Sildenafil
- Midazolam
- Triazolam

When KISQALI is co-administered with other medicinal products, the Summary of Product Characteristics of the other medicinal product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

SUBSTANCES THAT ARE SUBSTRATES OF TRANSPORTERS[1]

KISQALI has a potential to inhibit the activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP.

Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index, including but not limited to the following:

- Digoxin
- Pitavastatin
- Pravastatin
- Rosuvastatin
- Metformin

Anticipated interactions

MEDICINAL PRODUCTS THAT MAY PROLONG THE QT INTERVAL[1]

Co-administration of KISQALI with anti-arrhythmic medicinal products with a known potential to prolong the QT interval, including, but not limited to, the following, should be avoided:

- Amiodarone
- Disopyramide
- Procainamide
- Quinidine
- Sotalol

Co-administration of KISQALI with other medicinal products with a known potential to prolong the QT interval, including but not limited to the following, should be avoided:

- Chloroquine
- Halofantrine
- Clarithromycin
- Haloperidol
- Methadone
- Moxifloxacin
- Bepridil
- Pimozide
- Intravenous ondansetron

For a full list of potential interactions, please consult the Summary of Product Characteristics for KISQALI.

PRESCRIBING INFORMATION

Kisqali® ▼ (ribociclib succinate)

(Please refer to the SmPC before prescribing Kisqali)

Presentation: Film-coated tablet containing ribociclib succinate, equivalent to 200 mg ribociclib. **Indication**: Kisqali, in combination with an aromatase inhibitor, is indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy. **Dosage**: The recommended dose is 600 mg once daily; taken orally with or without food at the same time every day for 21 days, followed by 7 days off treatment, resulting in a complete cycle of 28 days. The treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. Kisqali should be used together with 2.5 mg letrozole or another aromatase inhibitor (AI). The AI should be taken orally once daily continuously throughout the 28-day cycle. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken. The next prescribing dose should be taken at the usual time. **Dose Modification**: Management of severe or intolerable adverse drug reactions may require temporary dose interruption, reduction or discontinuation of Kisqali (See Special Warnings & Precautions). Dose reduction should be achieved by decrements of 200 mg daily. If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued. *Full blood counts (FBC)* should be performed before and after initiating Kisqali treatment. FBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. For neutropenia, no dose modifications required for grade 1 or 2. For grade 3, interrupt the dose until recovery to grade ≤2, then resume at same dose level. If toxicity recurs at grade 3, interrupt the dose until recovery, then resume Kisqali and reduce by 1 dose level. For grade 3 febrile neutropenia interrupt the dose until recovery to grade ≤2, resume Kisqali and reduce by 1 dose level. For grade 4 interrupt the dose until recovery to grade ≤2, resume Kisqali and reduce by 1 dose level. *Liver function tests (LFTs)* should be performed before and after initiating Kisqali treatment. LFTs should be performed every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If grade ≤2 abnormalities are noted, more frequent monitoring is recommended. No dose adjustment is required for grade 1. For grade 2: if baseline at grade <2, interrupt until recovery to ≤ baseline grade, then resume Kisqali at same dose, and if grade 2 recurs, resume Kisqali at next lower dose level; if baseline at grade 2, no dose interruption. For grade 3: interrupt Kisqali until recovery to ≤ baseline grade then resume at next lower dose level. If grade 3 recurs, discontinue Kisqali. For grade 4: discontinue Kisqali. If patients develop ALT and/or AST >3xULN along with total bilirubin >2xULN irrespective of baseline grade, discontinue Kisqali. ECG should be assessed before and after initiating treatment with Kisqali. ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended. ECGs with QTcF >480 msec the dose should be interrupted. If the QTcF resolves to <481 msec, resume the treatment at same dose level and if QTcF >481 msec recurs, interrupt the dose until QTcF resolves to <481 and then resume Kisqali at the next lower dose level. If QTcF >500 msec on at least 2 separate ECGs, interrupt Kisqali until QTcF <481 msec then resume Kisqali at next lower dose level. If QTcF >500 msec or >60 msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali. For other toxicities no dose adjustment required for grade 1 or 2, initiate appropriate medical therapy and monitor as clinically indicated. For grade 3, interrupt until recovery to grade ≤1, then resume Kisqali at the same dose. If grade 3 recurs, resume Kisqali at the next lower dose level. For grade 4, discontinue Kisqali. Concomitant use of strong CYP3A4 inhibitors should be avoided and an alternative concomitant medicinal product with less potential to inhibit CYP3A4 inhibition should be considered. If patients must be given a strong CYP3A4 inhibitor concomitantly with ribociclib, the Kisqali dose should be reduced to 400 mg once daily. **Contraindications**: Hypersensitivity to the active substance or to peanut, soya or any other listed excipients. **Special Warnings and Precautions**: *Critical Visceral Disease*: The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease. *Neutropenia* Based on the severity of the neutropenia, Kisqali treatment may have to be interrupted, reduced or discontinued. *QT Interval prolongation*: Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali. The use of Kisqali with medicinal products known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval. Kisqali should be avoided in patients with long QT syndrome, significant cardiac disease and electrolyte abnormalities. *Hepatobiliary toxicity, CYP3A4 substrates, soya lecithin*: see other sections. Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman. Kisqali may have a minor influence on the ability to drive and use machinery; patients should be cautious in case they experience fatigue. **Undesirable Effects**: *Very common*: abdominal pain, abnormal liver function tests (ALT, AST & blood bilirubin increased), alopecia, anaemia, asthenia, back pain, constipation, decreased appetite, diarrhoea, dyspnoea, fatigue, headache, insomnia, leukopenia, lymphopenia, nausea, neutropenia, peripheral oedema, pruritus, pyrexia, rash, stomatitis, urinary tract infection and vomiting. *Common*: decreased weight, dry eye, dysgeusia, dyspepsia, electrocardiogram QT prolonged, epistaxis, erythema, febrile neutropenia, hepatotoxicity, hypocalcaemia, hypokalaemia, hypophosphataemia, increased lacrimation, increased blood creatinine, syncope and thrombocytopenia. **Interactions**: Ribociclib is primarily metabolised by CYP3A4. Medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of ribociclib. Ribociclib is a moderate to strong CYP3A4 inhibitor and may interact with medicinal substrates that are metabolised via CYP3A4, which can lead to increased serum concentrations of the concomitantly used medicinal product. Co-administration of Kisqali with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products and other medicinal products that are known to prolong the QT interval should be avoided. Please refer to the SmPC for other possible interactions.

Basic NHS Cost: 21 tablets = £983.33, 42 tablets = £1,966.67, 63 tablets = £2,950.00.

Marketing Authorisation (MA) Holder: Novartis Europharm Ltd, Frimley Business Park, Camberley, GU16 7SR, UK.

MA Number: EU/1/17/1221/001-012

Legal category: POM

Further information is available from Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK. Tel: 01276 692255.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Novartis on 01276 698370, at medinfo.uk@novartis.com or online through the patient safety information tool at https://psi.novartis.com

References:
1. KISQALI Summary of Product Characteristics.
2. US Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 4.03. 2010. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (Accessed July 2017).
3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *NEJM.* 2016; 375(18); 1738-1748.

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KISQALI® ribociclib

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