Prescribing information can be accessed via the QR code on the last page of this document.

FOR UK HCPs ONLY

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In eBC & aBC

KISQALI® (ribociclib) therapy management guide

Optimising KISQALI treatment for your eligible patients

Indications:[1]

Early breast cancer (eBC)

KISQALI in combination with an aromatase inhibitor (AI) is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative eBC at high risk of recurrence.

In pre/perimenopausal women, or in men, the AI should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Advanced breast cancer (aBC)

KISQALI is indicated for the treatment of women with HR+/HER2− locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine based therapy, or in women who have received prior endocrine therapy (ET).

In pre/perimenopausal women, the ET should be combined with a LHRH agonist.

KISQALI is not recommended to be used in combination with tamoxifen.[1]

aBC, advanced breast cancer; AI, aromatase inhibitor; eBC, early breast cancer; ET, endocrine therapy; HCP, healthcare professional; HR+/HER2−, hormone receptor-positive and human epidermal growth factor receptor 2-negative; LHRH, luteinising hormone-releasing hormone.

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 online through the pharmacovigilance intake (PVI) tool at **www.novartis.com/report** or alternatively email medinfo.uk@novartis.com or call 01276 698370.

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NOVARTIS

KISQALI® ribociclib

Introduction

KISQALI is a CDK4/6 inhibitor given for the treatment of HR+/ HER2– early, locally advanced or metastatic breast cancer in eligible patients.[1]

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

For full prescribing information, consult the KISQALI Summary of Product Characteristics (https://www.medicines.org.uk/emc/product/8110/smpc).

Indications[1]

Early breast cancer (eBC)

KISQALI in combination with an AI is indicated for the adjuvant treatment of patients with HR+/HER2– eBC at high risk of recurrence.

In pre/perimenopausal women, or in men, the AI should be combined with a LHRH agonist.

Advanced breast cancer (aBC)

KISQALI is indicated for the treatment of women with HR+/HER2– locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine based therapy, or in women who have received prior ET.

In pre/perimenopausal women, the ET should be combined with a LHRH agonist.

KISQALI is not recommended to be used in combination with tamoxifen.

Mechanism of action[1]

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

In vitro, KISQALI has been shown to induce G1-phase cell cycle arrest and reduce proliferation of breast cancer cells. *In vivo*, both KISQALI + letrozole and KISQALI + fulvestrant combinations resulted in tumour growth inhibition.

KISQALI is taken in combination with an AI (e.g., letrozole) or fulvestrant (a selective oestrogen receptor downregulator) to delay disease progression.

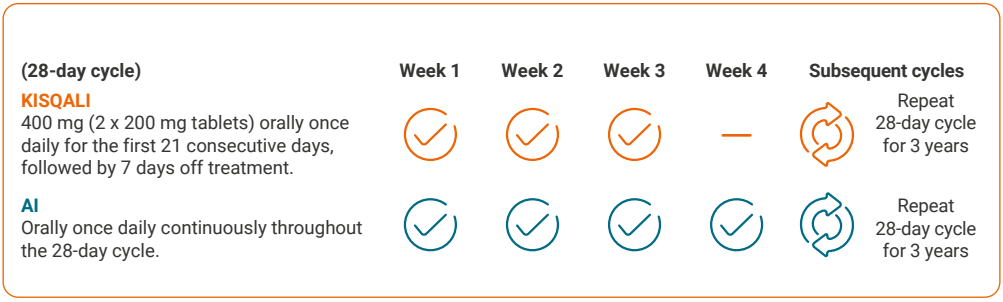
aBC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinases 4 and 6; eBC, early breast cancer; ET, endocrine therapy; G1, gap phase 1; HCP, healthcare professional; HR+/HER2–, hormone receptor-positive and human epidermal growth factor receptor 2-negative; LHRH, luteinising hormone-releasing hormone.

Contents

Dosing and administration

Once-daily dosing with KISQALI[1]

KISQALI in combination with an AI in eBC[1]



Please refer to the respective SmPC for recommended dose of chosen AI.

In pre/perimenopausal women, or in men, a LHRH agonist should be administered according to local clinical practice when given with KISQALI and an AI.[1]

KISQALI, an AI and a LHRH agonist can all be started at the same time.[1]

In patients with eBC, KISQALI should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur.[1]

AI, aromatase inhibitor; eBC, early breast cancer; LHRH, luteinising hormone-releasing hormone; SmPC, summary of product characteristics.

Please refer to Prescribing Information for important safety information.

KISQALI in combination with an AI in aBC[1]

(28-day cycle)	Week 1	Week 2	Week 3	Week 4	Subsequent cycles
KISQALI 600 mg (3 x 200 mg tablets) orally once daily for the first 21 consecutive days, followed by 7 days off treatment.	✓	✓	✓	—	Repeat 28-day cycle
AI Orally once daily continuously throughout the 28-day cycle.	✓	✓	✓	✓	Repeat 28-day cycle

Please refer to the respective SmPC for recommended dose of chosen AI.

In pre/perimenopausal women, a LHRH agonist should be administered according to local clinical practice when given with KISQALI and an AI.[1]

KISQALI, an AI and a LHRH agonist can all be started at the same time.[1]

KISQALI in combination with fulvestrant in aBC[1]

(28-day cycle)	Week 1	Week 2	Week 3	Week 4	Subsequent cycles
KISQALI 600 mg (3 x 200 mg tablets) orally once daily for the first 21 consecutive days, followed by 7 days off treatment.	✓	✓	✓	—	Repeat 28-day cycle
Fulvestrant Administered intramuscularly.	✓ Day 1 injection	—	✓ Day 15 injection (Cycle 1 only)	—	✓ Once monthly

Please refer to the SmPC of fulvestrant for additional details.

When given with KISQALI, the recommended dose of fulvestrant should be administered on Days 1, 15, 29 and once monthly thereafter. Please refer to the full SmPC for fulvestrant.

In pre/perimenopausal women, a LHRH agonist should be administered according to local clinical practice when given with KISQALI and fulvestrant.[1]

aBC, advanced beast cancer; AI, aromatase inhibitor; LHRH, luteinising hormone-releasing hormone; SmPC, summary of product characteristics.

Please refer to Prescribing Information for important safety information.

Dosing and administration (cont.)

Dose modification and adverse event management[1]

KISQALI offers adjustable dosing to manage adverse events (AEs).[1]

Dose modifications in eBC[1]

Recommended dose	Reduction
2 tablets (400 mg/day)	1 tablet (200 mg/day)

Dose modifications in aBC[1]

Recommended dose	First reduction	Second reduction
3 tablets (600 mg/day)	2 tablets (400 mg/day)	1 tablet (200 mg/day)

Each film-coated tablet contains 200 mg of ribociclib.[1]

Dose adjustments for AEs should be made in a stepwise order by reducing the number of tablets taken.[1]

Dose modification of KISQALI is recommended based on individual safety and tolerability.[1]

If dose reduction below 200 mg/day is required, permanently discontinue treatment.[1]

aBC, advanced breast cancer; AE, adverse event; eBC, early breast cancer.

Please refer to Prescribing Information for important safety information.

Recommended starting doses of KISQALI for special populations[1]

Renal impairment	eBC	aBC
Mild (eGFR 60 to <90 ml/min)	No dose adjustment required.	
Moderate (eGFR 30 to <60 ml/min)	No dose adjustment required.	
Severe (eGFR 15 to <30 ml/min)	The recommended starting dose is 200 mg/day. The efficacy of this starting dose has not been studied in these patients. **Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity.**	

Hepatic impairment	eBC
No dose adjustment required.	

Hepatic impairment	aBC
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	eBC	aBC
Paediatric population (aged <18 years)	The safety and efficacy of KISQALI in children and adolescents aged below 18 years has not been established and no data is available.	
Elderly (aged >65 years)	No dose adjustment required.	

Patients with moderate and severe hepatic impairment can have increased (less than 2-fold) exposure to KISQALI, and the starting dose of 400 mg KISQALI once daily is recommended.[1]

A reduced dose of KISQALI may be required when strong CYP3A4 inhibitors are concomitantly administered.[1]

Concomitant use of strong CYP3A4 inhibitors should be avoided. Dose adjustments with strong CYP3A4 inhibitors are detailed on page 8 of this guide.

aBC, advanced breast cancer; eBC, early breast cancer; eGFR, estimated glomerular filtration rate; CYP3A4, cytochrome P450 family A subfamily 4.

Guidance for drug-drug interactions and monitoring schedule

Drug-drug interactions[1]

KISQALI is primarily metabolised by CYP3A4. Certain medicines and foods can interact with CYP3A4 enzyme activity and may alter the pharmacokinetics of KISQALI. Additionally, KISQALI is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose.[1]

When KISQALI is co-administered with other medicinal products, the SmPC of the other medicinal product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. **Caution is recommended** in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index and the SmPC of the other product should be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.[1]

Not all products mentioned in the table below are licensed. Please refer to individual SmPCs.

Category[1]	Examples (including, but not limited to)[1]
Strong CYP3A4 inhibitors **Should be avoided** •If coadministration with KISQALI cannot be avoided, the daily dose of KISQALI should be reduced to the next lower dose •If the CYP3A4 inhibitor is discontinued, resume the dose of KISQALI used prior to the initiation of the CYP3A4 inhibitor, after waiting at least 5 half-lives of the CYP3A4 inhibitor No clinical data with this dose adjustment are available. If dose reduction below 200 mg/day is required, 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 KISQALI-related adverse reactions is recommended. In the event of KISQALI-related toxicity, the dose should be modified or treatment should be interrupted until toxicity is resolved.	Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, posaconazole, voriconazole, verapamil, grapefruit, grapefruit juice, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir
Moderate CYP3A4 inhibitors No dose adjustments of KISQALI are required at initiation of treatment with mild or moderate CYP3A4 inhibitors; however, monitoring of KISQALI-related adverse reactions is recommended.	
Strong CYP3A4 inducers Strong CYP3A4 inducers **should be avoided** •An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered	Rifampicin, carbamazepine, phenytoin, St. John's Wort *(Hypericum perforatum)*
Moderate CYP3A4 inducers Concomitant use of moderate CYP3A4 inducers may lead to decreased KISQALI exposure and consequently a risk of impaired efficacy, in particular in patients treated with KISQALI at 400 mg or 200 mg once daily.	
CYP3A4 substrates **Caution is recommended** with sensitive CYP3A4 substrates with a narrow therapeutic index.	Ciclosporin, sirolimus, tacrolimus, everolimus, alfentanil, fentanyl

Drug-drug interaction studies between KISQALI and oral contraceptives have not been conducted.[1]

Co-administration of KISQALI with medicinal products that elevate the gastric pH has not been evaluated in a clinical study.[1]

For a list of medications and components that are known to interact with CYP3A4 enzyme activity and basic heart function, please see the SmPC.

CYP3A4, cytochrome P450 family A, subfamily 4; mTOR, mammalian target of rapamycin; SmPC, summary of product characteristics.

Please refer to Prescribing Information for important safety information.

Category[1]	Examples (including, but not limited to)[1]
Concomitant administration of KISQALI at the 600 mg dose with certain CYP3A4 substrates **should be avoided** • The SmPC of the other medicinal product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.	Alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam and triazolam
Antiarrhythmics and medicines known to prolong QT interval **Should be avoided**	Amiodarone, disopyramide, procainamide, quinidine, sotalol; azithromycin, ciprofloxacin, clarithromycin, levofloxacin, moxifloxacin, chloroquine, halofantrine, haloperidol, pimozide, bepridil, methadone, ondansetron (IV)) KISQALI is not recommended to be used in combination with tamoxifen
Drug transporters **Caution and monitoring for toxicity** are advised with concomitant administration with sensitive substrates of transporters which exhibit a narrow therapeutic index.	Digoxin, pravastatin, rosuvastatin, pitavastatin, metformin

Recommended monitoring schedule[1]

		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	
Blood test	CBC LFT	Baseline and mid-cycle (to be conducted every 2 weeks)	Baseline and mid-cycle (to be conducted every 2 weeks)	Beginning of each cycle				Monitoring as clinically indicated beyond Cycle 6
Blood test	Electrolytes	Baseline	Beginning of each cycle					
ECGs	QTcF	Baseline and mid-cycle (approx. Day 14)	As clinically indicated					

Any additional monitoring should be performed as clinically indicated.

Additional monitoring recommendations:[1]

Blood tests:

- LFTs: If grade ≥2 abnormalities are noted, more frequent monitoring is recommended
- Electrolytes: Correct any electrolyte abnormalities prior to and during treatment with KISQALI
- Baseline and mid-cycle monitoring: Perform baseline assessment prior to treatment initiation

ECGs:

- QTcF/baseline and mid-cycle monitoring: KISQALI should only be initiated in patients with QTcF <450 msec. In case of QTcF prolongation during therapy, more frequent monitoring is recommended

CBC, complete blood count; CYP3A4, cytochrome P450 family A, subfamily 4; ECG, electrocardiogram; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; IV, intravenous; LFT, liver function test; QTcF, QT interval corrected by Fridericia's formula; SmPC, summary of product characteristics.

Managing neutropenia

Clinical incidence[1]

Neutropenia is a very common AE associated with KISQALI treatment (occurring at a frequency of ≥1/10 patients) and was the most frequently reported AE across all MONALEESA studies and in the NATALEE study.[1–7]

eBC: Clinical incidence in patients who received KISQALI + NSAI in the NATALEE study[1]

In the NATALEE study, febrile neutropenia was reported in 0.3% of patients exposed to KISQALI + NSAI

- **Median time to onset** (Grades 2–4*) was **0.6 months (~18 days)**
- **Median time to resolution**† (Grades ≥3) was **0.3 months (~9 days)**

aBC: Clinical incidence in patients who received KISQALI plus any combination across all MONALEESA trials[1]

In the MONALEESA trials, febrile neutropenia was reported in 1.7% of patients

- **Median time to onset** (Grades 2–4*) was **17 days**
- **Median time to resolution**† (Grades ≥3) was **12 days**

*Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03: grade 1 or 2 neutropenia: ANC 1000/mm3 to ≤LLN; grade 3 neutropenia: ANC 500 to <1000/mm3; grade 3 febrile neutropenia: grade 3 neutropenia with a single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection); grade 4 neutropenia: ANC <500/mm^3.[1,8]

†Decrease in neutrophil count, based on laboratory findings to normalisation or <grade 3, following treatment interruption and/or reduction and/or discontinuation.[1]

AE, adverse event; ANC, absolute neutrophil counts; CTCAE, common terminology criteria for adverse events; eBC, early breast cancer; LLN, lower limit of normal; NSAI, non-steroidal aromatase inhibitor.

Please refer to Prescribing Information for important safety information.

Neutropenia management algorithm[1]

Full blood counts should be performed before initiating treatment with KISQALI.

After initiation of KISQALI, full blood counts 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/mm^3 to ≤LLN (Grades 1 or 2*)	ANC 500–<1000/mm^3 (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/mm^3 (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 CTCAE Version 4.03.[1,8]

ANC, absolute neutrophil count; CTCAE, common terminology criteria for adverse events; LLN, lower limit of normal.

Managing hepatobiliary toxicity

Clinical incidence[1]

Hepatobiliary toxicity events* are common AEs associated with KISQALI treatment (occurring at a frequency of ≥1/100 patients, but <1/10 patients). Abnormal LFTs are very common AEs (occurring at a frequency of ≥1/10 patients).[1]

eBC: Clinical incidence in patients who received KISQALI + NSAI in the NATALEE study[1,4]

Grades 3/4:†

- **Median time to onset** (Grades 3/4*) was **2.8 months (~86 days)**
- **Median time to resolution‡** (Grades 3/4*) was **0.7 months (~21 days)**
- Discontinuation of treatment with KISQALI + NSAI due to abnormal LFTs or hepatotoxicity occurred in 8.9% and 0.1% of patients, respectively

aBC: Clinical incidence in patients who received KISQALI plus any combination across all MONALEESA trials[1]

Grades 3/4:†

- **Median time to onset** (Grades 3/4*) was **92 days**
- **Median time to resolution†** (Grades ≥3*) was **21 days**
- Discontinuation of KISQALI plus any combination due to abnormal LFTs or hepatotoxicity occurred in 2.4% and 0.3% of patients, respectively

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. Recommendations for patients who have grade ≥3 ALT/AST elevation at baseline have not been established.[1]

*Hepatotoxicity included hepatocellular injury, drug-induced liver injury, hepatotoxicity, hepatic failure and autoimmune hepatitis (of which there was a single case).[1]

†Grading according to CTCAE Version 4.03: grade 1 ALT/AST elevation: >ULN–3 x ULN; grade 2 ALT/AST elevation: >3–5 x ULN; grade 3 ALT/AST elevation: >5–20 x ULN; grade 4 ALT/AST elevation: >20 x ULN.[1,8]

‡Defined as normalisation or resolution to grade ≤2.[1]

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; eBC, early breast cancer; LFT, liver function test; NSAI, non-steroidal aromatase inhibitor; ULN, upper limit of normal.

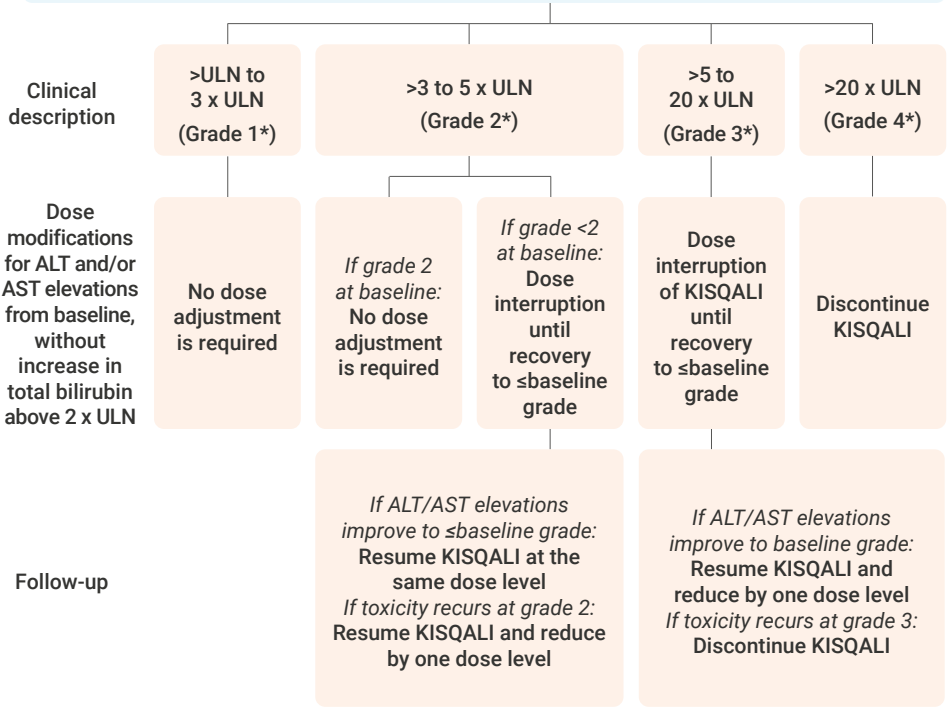
Please refer to Prescribing Information for important safety information.

Hepatobiliary toxicity management algorithm[1]

LFTs should be performed before initiating treatment with KISQALI.

After initiation, 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.



If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue KISQALI.[1]

If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.[1]

*Grading according to CTCAE Version 4.03.[1,8]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; LFT, liver function test; ULN, upper limit of normal.

Managing QT prolongation

Clinical incidence[1]

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

eBC: Clinical incidence in patients who received KISQALI + NSAI in the NATALEE study[1]

Incidence rates[1]

- At least one QTcF >480 msec (post-baseline): **0.4%**
- QTcF >500 msec (post-baseline): **0.1%**
- QTcF >60 msec increase from baseline: **0.8%**

In the NATALEE study, 5.3% of patients in the KISQALI + NSAI arm vs 1.4% of patients in the NSAI alone arm reported events of QT interval prolongation.[1]

Median time to onset for QTcF prolongation >480 msec[1]

15 days

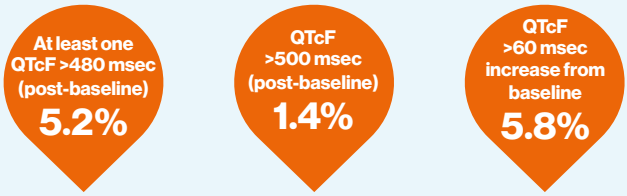
Reversible with dose interruption and/or reduction

NSAI, non-steroidal aromatase inhibitor; QTcF, QT interval corrected by Fredericia's formula.

Please refer to Prescribing Information for important safety information.

aBC: Clinical incidence in patients who received KISQALI + ET across all MONALEESA trials[1]

Incidence rates



In the MONALEESA trials, at least one event of QT interval prolongation was reported in 9.3% of patients in the KISQALI + AI or fulvestrant arms vs 3.5% in the placebo + AI or fulvestrant arms.[1]

Median time to onset for QTcF prologation >480 msec

Reversible with dose interruption and/or reduction

There were no reported cases of *torsade de pointes*.[1]

Based on the severity of QT interval prolongation, treatment with KISQALI may have to be interrupted, reduced or discontinued, as described on the next page.[1]

Dose interruptions/adjustments were reported in 2.9% of KISQALI + AI or fulvestrant treated patients due to electrocardiogram QT prolonged and syncope.[1]

QT interval prolongation in eBC and aBC patients

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.[1] If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg once daily.[1]

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:[1]

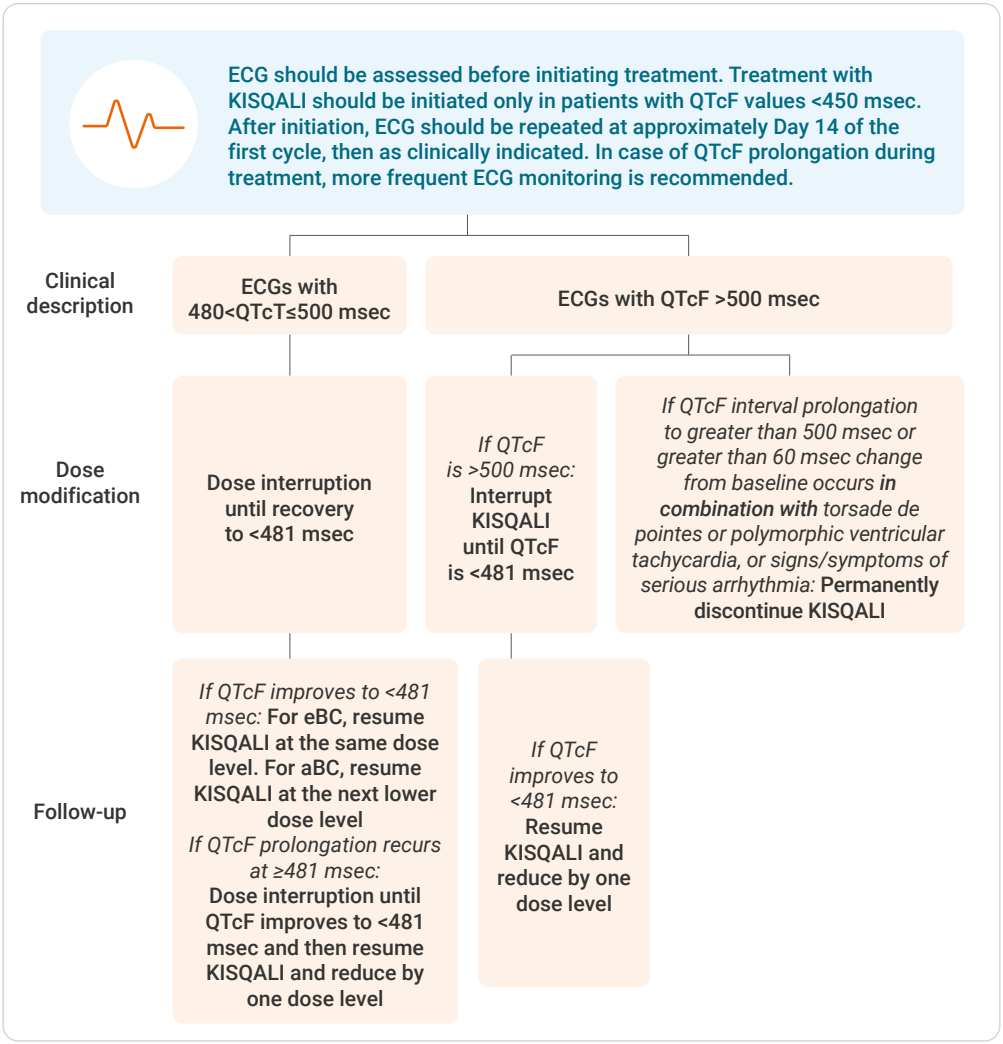
- **Long QT syndrome**
- **Uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias**
- **Electrolyte abnormalities**

aBC, advanced breast cancer; AI, aromatase inhibitor; CYP3A4, cytochrome P450 family A, subfamily 4; eBC, early breast cancer; ET, endocrine therapy; QTc, corrected QT interval; QTcF, QT interval corrected by Fridericia's formula.

Please refer to Prescribing Information for important safety information.

Managing QT prolongation (cont.)

QT prolongation management algorithm[1]



If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.[1]

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 and during treatment with KISQALI.[1]

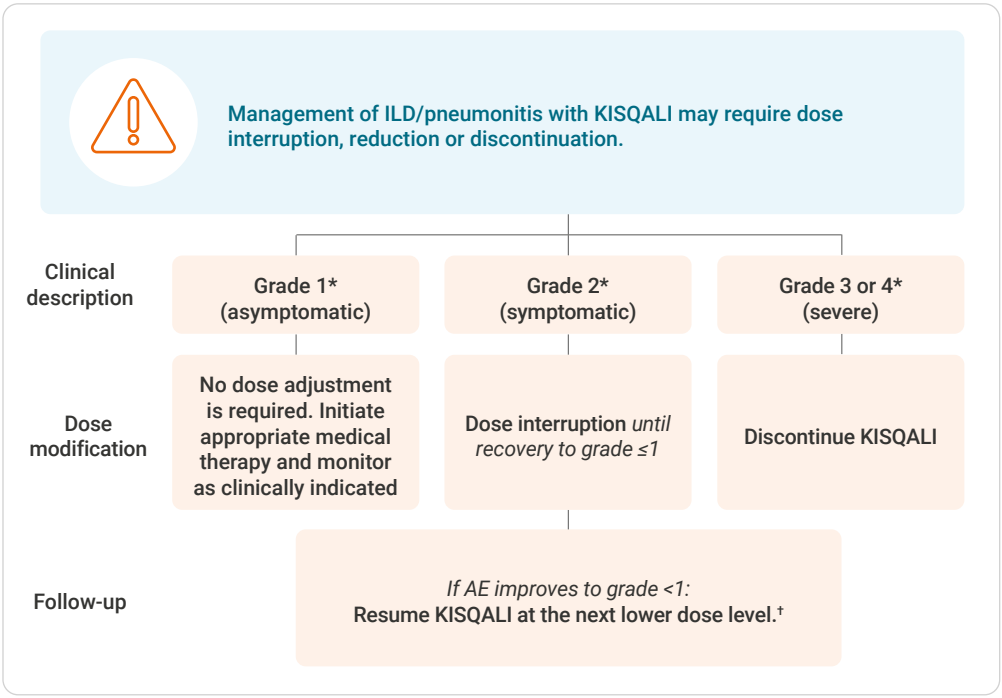
ECG, electrocardiogram; QTcF, QT interval corrected by Fridericia's formula.

Managing interstitial lung disease/ pneumonitis

Clinical incidence

ILD/pneumonitis is a common AE associated with KISQALI. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough and dyspnoea and dose modifications should be managed in accordance with Table 5 of the SmPC.[1]

ILD/pneumonitis management algorithm[1]



If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.[1]

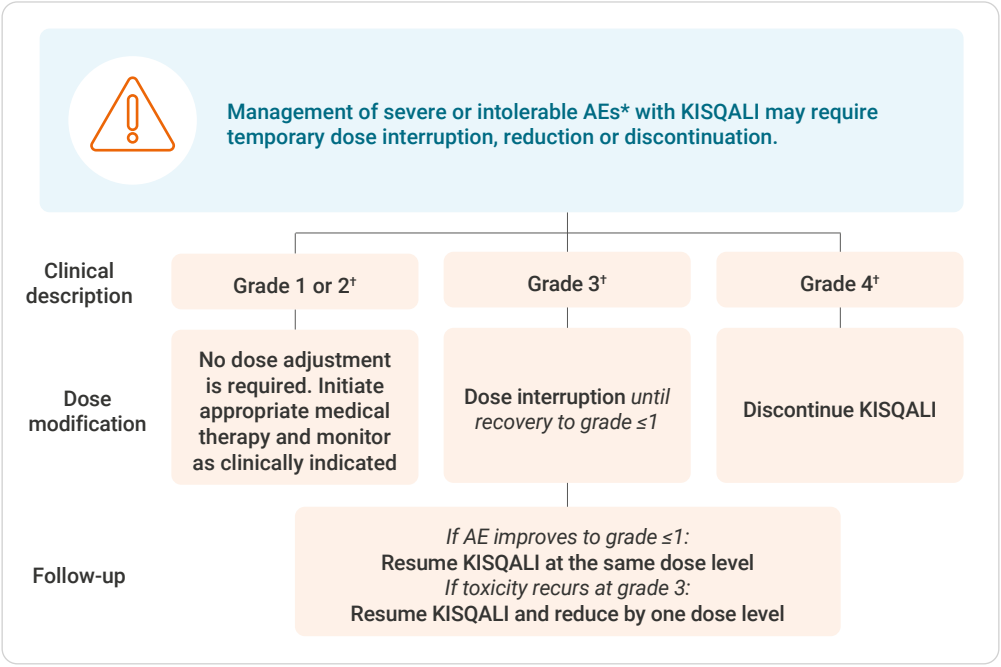
*Grading according to CTCAE Version 4.03.[1,8]
†An individualised benefit-risk assessment should be performed when considering resuming KISQALI.[1]

AE, adverse event; CTCAE, common terminology criteria for adverse events; ILD, interstitial lung disease; SmPC, summary of product characteristics.

Please refer to Prescribing Information for important safety information.

General adverse events management

General AEs management algorithm[1]



If dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.[1]

Refer to the SmPC for the co-administered AI, fulvestrant or LHRH agonist for dose modification guidelines and other relevant safety information in the event of toxicity.[1]

*Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis.[1]
†Grading according to CTCAE Version 4.03.[1,8]

AE, adverse event; AI, aromatase inhibitor; CTCAE, common terminology criteria for adverse events; LHRH, luteinising hormone-releasing hormone; SmPC, summary of product characteristics.

Please refer to Prescribing Information for important safety information.

Contraindications and other special warnings and precautions

Contraindications[1]

Hypersensitivity to the active substance or to peanut, soya or any of the excipients listed in section 6.1 of the SmPC.

Effects during pregnancy and lactation, and on fertility[1]

KISQALI is indicated for use in pre/perimenopausal or postmenopausal women, so 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.

Based on animal studies, KISQALI may impair fertility in males of reproductive potential.

Women of childbearing potential who are receiving KISQALI should use effective contraception (e.g., double-barrier contraception) during therapy and for at least 21 days after stopping treatment with KISQALI.

KISQALI is not recommended during pregnancy and in women of childbearing potential not using contraception.

Patients receiving KISQALI should not breastfeed for at least 21 days after the last dose.

Effects on ability to drive and use machines[1]

KISQALI may have minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue, dizziness or vertigo during treatment with KISQALI.

Critical visceral disease[1]

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

ILD/pneumonitis[1]

ILD/pneumonitis has been commonly reported with KISQALI and may require treatment with KISQALI to be interrupted, reduced or discontinued. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough and dyspnoea.

Severe cutaneous reactions[1]

Toxic epidermal necrolysis has been reported in KISQALI treatment during post-marketing experience. If signs and symptoms suggestive of severe cutaneous reactions (e.g., progressive widespread skin rash often with blisters or mucosal lesions) appear, KISQALI should be discontinued immediately.

Blood creatinine increase and severe renal impairment[1]

KISQALI may cause blood creatinine increase as an inhibitor of the renal transporters organic cation transporter 2 and multidrug and toxin extrusion protein 1, which are involved in the active secretion of creatinine from the proximal tubules. In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment. The recommended starting dose of 200 mg for patients with severe renal impairment is estimated to result in approximately 45% lower exposure compared with the standard starting dose in patients with normal renal function.

KISQALI has not been studied in breast cancer patients with severe renal impairment, and the efficacy at the 200 mg starting dose has not been studied. Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity.

Soya lecithin[1]

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

Tamoxifen[1]

Data from a clinical study in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2-fold following co-administration with KISQALI. **KISQALI is not recommended to be used in combination with tamoxifen.**

ILD, interstitial lung disease; SmPC, summary of product characteristics.

Please refer to Prescribing Information for important safety information.

Adverse events in the Summary of Product Characteristics

Common AEs in eBC[1]

The most commons AEs reported with KISQALI + AI were neutropenia, infections, nausea, headache, fatigue, leukopenia and abnormal LFTs.

Permanent discontinuation was reported in 19.7% of eBC patients receiving KISQALI + AI in the Phase III clinical trial.[1]

Common AEs in aBC[1]

The most common AEs were neutropenia, infections, nausea, fatigue, diarrhoea, leukopenia, vomiting, headache, constipation, alopecia, cough, rash, back pain, anaemia and abnormal LFTs.

Permanent discontinuation was reported in 8.7% of aBC patients receiving KISQALI + ET* in Phase III clinical trials.[1]

AEs reported in the Phase III clinical studies and during post-marketing experience[1]

Corresponding frequency category for each AE based on the CIOMS III: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from the available data).[1]

Frequency and AE	eBC (with a starting dose of 400 mg KISQALI)	aBC (with a starting dose of 600 mg KISQALI)
Infections and infestations		
Very common	Infections†	Infections†
Blood and lymphatic system disorders		
Very common	Neutropenia, leukopenia	Neutropenia, leukopenia, anaemia, lymphopenia
Common	Anaemia, thrombocytopenia, lymphopenia	Thrombocytopenia, febrile neutropenia
Uncommon	Febrile neutropenia	–
Metabolism and nutrition disorders		
Very common	–	Appetite decreased
Common	Hypocalcaemia, hypokalaemia, appetite decreased	Hypocalcaemia, hypokalaemia, hypophosphataemia
Nervous system disorders		
Very common	Headache	Headache, dizziness
Common	Dizziness	Vertigo
Eye disorders		
Common	–	Lacrimation increased, dry eye

*KISQALI is not recommended for use with tamoxifen.[1]
†Infections: urinary tract infections, respiratory tract infections, gastroenteritis, sepsis (<1%).[1]

aBC, advanced breast cancer; AE, adverse event; CIOMS, Council for International Organisations of Medical Sciences; eBC, early breast cancer; LFT, liver function test.

Please refer to Prescribing Information for important safety information.

Frequency and AE	eBC (with a starting dose of 400 mg KISQALI)	aBC (with a starting dose of 600 mg KISQALI)
Cardiac disorders		
Common	–	Syncope
Respiratory, thoracic and mediastinal disorders		
Very common	Cough	Dyspnoea, cough
Common	Dyspnoea, ILD/pneumonitis	ILD/pneumonitis
Gastrointestinal disorders		
Very common	Nausea, diarrhoea, constipation, abdominal pain*	Nausea, diarrhoea, vomiting, constipation, stomatitis, abdominal pain,* dyspepsia
Common	Vomiting, stomatitis†	Dysgeusia
Hepatobiliary disorders		
Common	Hepatotoxicity‡	Hepatotoxicity‡
Skin and subcutaneous tissue disorders		
Very common	Alopecia	Alopecia, rash,§ pruritus
Common	Rash,§ pruritus	Dry skin, erythema, vitiligo
Rare	–	Erythema multiforme
Not known	–	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		
Very common	–	Back pain
General disorders and administration site conditions		
Very common	Fatigue, asthenia, pyrexia	Fatigue, peripheral oedema, pyrexia, asthenia
Common	Peripheral oedema, oropharyngeal pain	Oropharyngeal pain, dry mouth
Investigations		
Very common	Abnormal LFTs¶	Abnormal LFTs¶
Common	Blood creatinine increased, ECG QT prolonged	Blood creatinine increased, ECG QT prolonged

Adapted from KISQALI Summary of Product Characteristics.[1]

For further safety information, please refer to the SmPC.[1]

*Abdominal pain: abdominal pain, abdominal pain upper.[1]
†Stomatitis for early breast cancer includes: stomatitis, mucositis.[1]
‡Hepatotoxicity: hepatic cytolysis, hepatocellular injury, drug-induced liver injury (<1%), hepatotoxicity, hepatic failure, autoimmune hepatitis (single case).[1]
§Rash: rash, rash maculopapular, rash pruritic.[1]
¶Abnormal LFTs: ALT increased, AST increased, blood bilirubin increased.[1]

aBC, advanced breast cancer; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eBC, early breast cancer; ECG, electrocardiogram; ET, endocrine therapy; ILD, interstitial lung disease; LFT, liver function test; SmPC, summary of product characteristics.

Safety profile in eBC and aBC

Established safety profile with KISQALI + NSAI in eBC:[3,4,9]

In the NATALEE study, KISQALI + NSAI had a generally manageable & consistent safety profile vs NSAI alone, with no new safety signals identified at 3 years.[4]

KISQALI + NSAI[1]	Dose reductions due to AEs[1]	Discontinuation due to AEs[1]
KISQALI + NSAI (n=2525)[4] %	22.8	19.7

- AEs generally occurred early in the treatment, allowing for prompt dose adjustments[10]
- For KISQALI, the median time to discontinuation due to AEs was 4 months[10]
- The majority of grade ≥3 AEs were asymptomatic laboratory findings that were generally identifiable and manageable[10]

AE, adverse event; eBC, early breast cancer; NSAI, non-steroidal aromatase inhibitor.

Please consult the Summary of Product Characteristics for the full KISQALI safety and tolerability profile.

Established safety profile with KISQALI + ET in aBC:[11,12]

Across MONALEESA-2, -3 and -7, the majority of AEs were generally manageable with dose modifications, allowing most patients to remain on treatment.[2,6,7]

MONALEESA-7

KISQALI + NSAI + LHRH agonist (subgroup)[5]	Dose reductions due to AEs	Discontinuation due to AEs
KISQALI + NSAI + LHRH agonist (n=248) %	33	7
Placebo + NSAI + LHRH agonist (n=247) %	4	3

MONALEESA-3

KISQALI + fulvestrant[6]	Dose reductions due to AEs	Discontinuation due to AEs
KISQALI + fulvestrant (n=483) % (n)	33 (160)	9 (41)
Placebo + fulvestrant (n=241) % (n)	3 (8)	4 (10)

MONALEESA-2

KISQALI + AI[7]	Dose reductions due to AEs	Discontinuation due to AEs
KISQALI + AI (n=334) % (n)	55 (182)	8 (27)
Placebo + AI (n=330) % (n)	4 (14)	2 (8)

All figures rounded to the nearest 1%.

AE, adverse event; LHRH, luteinising hormone-releasing hormone; NSAI, non-steroidal aromatase inhibitor.

Please refer to Prescribing Information for important safety information.

Adverse events in eBC

NATALEE | men or premenopausal and postmenopausal patients

Adjuvant therapy with an NSAI

AEs occurring in ≥15% of patients	KISQALI + NSAI n=2525				NSAI n=2442			
	Grade 3	Grade 4	Grade 5	Any grades	Grade 3	Grade 4	Grade 5	Any grades
Neutropenia*	42.2%	2.1%	0	62.5%	0.8%	0.1%	0	4.6%
Arthralgia	1.0%	0	0	37.3%	1.3%	0	0	43.3%
Nausea	0.2%	0	0	23.3%	<0.1%	0	0	7.8%
Headache	0.4%	0	0	22.8%	0.2%	0	0	17.0%
Fatigue	0.8%	0	0	22.3%	0.2%	0	0	13.2%
SARS-CoV-2 test positive	0	0	0	21.1%	0	0	0	13.6%
COVID-19	0.7%	0	0.1%	21.3%	0.5%	0	<0.1%	14.1%
Increased ALT	6.3%	1.3%	0	19.5%	0.7%	<0.1%	0	5.6%
Hot flush	0.2%	0	0	19.2%	0.1%	0	0	20.0%
Asthenia	0.6%	0	0	17.0%	0.1%	0	0	11.9%
Increased AST	4.0%	0.7%	0	16.9%	0.5%	0	0	5.7%
Alopecia	0	0	0	15.0%	0	0	0	4.5%

Adapted from Hortobagyi GN, et al. 2024.[4]

*This is a grouped term that combines neutropenia and neutrophil count decreases.[4]

AE, adverse event; ALT, alanine aminotransferase; AST aspartate aminotransferase; COVID-19, coronavirus disease 19; eBC, early breast cancer. NSAI, non-steroidal aromatase inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Please refer to Prescribing Information for important safety information.

Adverse events in aBC

MONALEESA-7 | Pre/perimenopausal patients

First line with an NSAI + LHRH agonist (subgroup)

AEs occurring in ≥20% of KISQALI patients[5]	KISQALI + NSAI + LHRH agonist n=248			Placebo + NSAI + LHRH agonist n=247		
	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
Neutropenia*	55%	10%	78%	3%	<1%	8%
Arthralgia	1%	0%	33%	1%	0%	29%
Hot flush	<1%	0%	31%	0%	0%	30%
Nausea	0%	0%	31%	0%	0%	20%
Leukopenia†	15%	1%	30%	1%	0%	5%
Fatigue	1%	0%	23%	0%	0%	25%
Headache	0%	0%	23%	<1%	0%	24%
Alopecia	0%	0%	21%	0%	0%	13%
Diarrhoea	2%	0%	20%	0%	0%	19%

Figures rounded to the nearest 1%.

Adapted from Bardia A, et al. 2018.[5]

*Neutropenia includes decreased neutrophil count and febrile neutropenia.[5]

†Leukopenia includes decreased white blood cell count, lymphopenia and decreased lymphocyte count.[5]

AE, adverse event; LHRH, luteinising hormone-releasing hormone; NSAI, non-steroidal aromatase inhibitor.

Please refer to Prescribing Information for important safety information.

Adverse events in aBC (cont.)

MONALEESA-3 | Postmenopausal patients

First line and second line with fulvestrant

AEs occurring in ≥20% of KISQALI patients[6]	KISQALI + fulvestrant n=483			Placebo + fulvestrant n=241		
	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
Neutropenia*	47%	7%	70%	0%	0%	2%
Nausea	1%	0%	45%	1%	0%	28%
Fatigue	2%	0%	32%	<1%	0%	33%
Diarrhoea	1%	0%	29%	1%	0%	20%
Leukopenia†	14%	1%	28%	0%	0%	2%
Vomiting	1%	0%	27%	0%	0%	13%
Constipation	1%	0%	25%	0%	0%	12%
Arthralgia	1%	0%	24%	<1%	0%	27%
Cough	0%	0%	22%	0%	0%	15%
Headache	1%	0%	22%	<1%	0%	20%
Pruritus	<1%	0%	20%	0%	0%	7%

Figures rounded to the nearest 1%.

Adapted from Slamon DJ, et al. 2018.[6]

*Neutropenia includes neutropenia, decreased neutrophil count, febrile neutropenia and neutropenic sepsis.[6]

†Leukopenia includes leukopenia, decreased white blood cell count, lymphopenia and decreased lymphocyte count.[6]

AE, adverse event.

Please refer to Prescribing Information for important safety information.

MONALEESA-2 | Postmenopausal patients

First line with an AI

AEs occurring in ≥20% of KISQALI patients[7]	KISQALI + AI n=334			Placebo + AI n=330		
	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
Neutropenia*	52%	10%	77%	1%	0%	6%
Nausea	2%	0%	53%	1%	0%	31%
Fatigue	3%	<1%	41%	1%	0%	32%
Diarrhoea	2%	0%	38%	1%	0%	25%
Alopecia	0%	0%	34%	0%	0%	16%
Vomiting	4%	0%	34%	1%	0%	17%
Arthralgia	1%	<1%	33%	1%	0%	33%
Leukopenia†	20%	1%	33%	1%	0%	5%
Headache	<1%	0%	27%	1%	0%	21%
Constipation	1%	0%	28%	0%	0%	22%
Hot flush	<1%	0%	25%	0%	0%	26%
Back pain	3%	0%	24%	<1%	0%	20%
Cough	0%	0%	23%	0%	0%	21%
Rash‡	2%	0%	22%	0%	0%	9%
Anaemia§	2%	1%	21%	1%	0%	6%
Decreased appetite	2%	0%	21%	<1%	0%	16%
Abnormal LFTs‖	8%	2%	20%	2%	0%	6%

Figures rounded to the nearest 1%.

Adapted from Hortobagyi GN, et al. 2018.[7]

*Includes neutropenia, decreased neutrophil count and granulocytopenia.[7]
†Includes decreased white blood cell count and leukopenia.[7]
‡Includes rash and maculopapular rash.[7]
§Includes anaemia, decreased haemoglobin and macrocytic anaemia.[7]
‖Includes increased ALT, increased AST and increased blood bilirubin.[7]

AE, adverse event; AI, aromatase inhibitor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test.

Please refer to Prescribing Information for important safety information.

KISQALI®
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