AUSTRALIAN PRODUCT INFORMATION - KISQALI® (ribociclib) tablets

1. NAME OF THE MEDICINE

Ribociclib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Each film coated tablet contains ribociclib succinate equivalent to 200 mg ribociclib.

Excipients

See section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Light greyish violet, unscored, round (approx. diameter: 11.1 mm), curved film-coated tablet with bevelled edges; debossed with "RIC" on one side and "NVR" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

4.2 Dose and method of administration

Treatment with KISQALI should be initiated by a physician experienced in the use of anticancer therapies.

Monitoring for adverse drug reactions (ADRs) is required, including full blood counts, LFTs, serum electrolytes, and ECG; dose modification (delay, reduction) or cessation may be required (see Tables 1-5).

Dose

KISQALI

The recommended dose of KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days, followed by 7 days off treatment, resulting in a complete cycle of 28 days. KISQALI may be taken with or without food (see section 4.5 Interactions with other medicines and other forms of interaction). Treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Aromatase inhibitor

When co-administered with KISQALI, the aromatase inhibitor is taken daily throughout the 28-day cycle. Please refer to the full Product Information for the aromatase inhibitor dosing regimen.

Patients should be encouraged to take their dose of KISQALI and aromatase inhibitor at approximately the same time each day, preferably in the morning.

Fulvestrant

When co-administered with KISQALI, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the full Product Information of fulvestrant.

Luteinising hormone-releasing hormone (LHRH) agonist

In pre- or perimenopausal women, the endocrine therapy should be co-administered with a luteinising hormone-releasing hormone (LHRH) agonist, according to current clinical practice standards.

Dose modifications

Management of severe or intolerable ADRs may require temporary dose interruption, dose reduction, or permanent discontinuation of KISQALI. If dose reduction is required, the recommended dose reduction guidelines are listed in Table 1.

Table 1 Recommended dose modification guidelines

	Dose	Number of Tablets
Starting dose	600 mg/day	3 × 200 mg tablets
First dose reduction	400 mg/day	2 × 200 mg tablets
Second dose reduction	200 mg*/day	1 × 200 mg tablets

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

Refer to the full Product Information of co-administered medicines (aromatase inhibitor, fulvestrant or LHRH agonist) for dose modification guidelines and other relevant safety information in the event of toxicity.

Tables 2 to 5 provide recommendations for dose interruption, reduction, or discontinuation of KISQALI in the management of specific ADRs. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (undesirable effects)).

Table 2 Dose modification and management for QT prolongation

On treatment ECGs with QTcF value of:	Recommendations
>480 ms	1. The dose should be interrupted 2. If QTcF prolongation resolves to <481 ms resume treatment at the next lower dose level; 3. If QTcF ≥481 ms recurs, dose interrupt until QTcF <481 ms, and then resume KISQALI at next lower dose level
>500 ms	Interrupt KISQALI until QTcF <481 ms then resume KISQALI at next lower dose level

On treatment ECGs with QTcF value of:	Recommendations
>500 ms or >60 ms change from baseline **With either:** • *Torsades de Pointes* **or** • polymorphic ventricular tachycardia **or** • unexplained syncope **or** • signs/symptoms of serious arrhythmia	Permanently discontinue KISQALI
ECG should be performed prior to initiation, repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. In patients with higher risk of QTcF prolongation or ventricular arrhythmias, more frequent ECG monitoring is recommended.	
Serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be performed prior to initiation of treatment and at the beginning of the next 5 cycles, with abnormalities corrected prior to commencement/ resumption of treatment. Cycle commencement must be accompanied by active review of all concomitantly administered medicines.	
In case of QTcF prolongation at any given time during treatment: • Perform analysis of serum electrolytes (K^+, Ca^{2+}, PO_4^{3-}, Mg^{2+}). If outside the normal range, interrupt ribociclib treatment, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval • More frequent ECG monitoring is recommended, e.g. 7 and 14 days after resumption of KISQALI	

Table 3 Dose modification and management for neutropenia and febrile neutropenia

	Grade 1 or 2 (ANC 1000/mm^3 – <LLN)	**Grade 3** (ANC 500 - <1000/mm^3)	**Grade 3 febrile* neutropenia**	**Grade 4**** (ANC <500/mm^3)
	No dose adjustment is required.	Dose interruption until recovery to grade ≤2. Resume KISQALI at the same dose level. If toxicity recurs at grade 3, dose interruption until recovery, then resume KISQALI at the next lower dose level.	Dose interruption until recovery of neutropenia to grade ≤2. Resume KISQALI at the next lower dose level.	Dose interruption until recovery to grade ≤2. Resume KISQALI at the next lower dose level.
Full (FBC) should be performed before initiating treatment with KISQALI. After initiating treatment with KISQALI, FBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.				
*****Grade 3 neutropenia with a single episode of fever >38.3°C (or) above 38°C for more than one hour and/or concurrent infection Grading according to CTCAE Version 4.0. CTCAE=Common Terminology Criteria for Adverse Events. ANC = absolute neutrophil count; LLN = lower limit of normal				

Table 4 Dose modification and management for hepatobiliary toxicity

	Grade 1 (>ULN – 3 x ULN)	Grade 2 (>3 to 5 x ULN)	Grade 3 (>5 to 20 x ULN)	Grade 4 (>20 x ULN)
AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN	No dose adjustment is required.	**Baseline at Grade ≤2:** Dose interruption until recovery to ≤baseline grade, then resume KISQALI at same dose level. If grade 2 recurs, resume KISQALI at next lower dose level. **Baseline Grade = 2:** No dose interruption.	Dose interruption until recovery to ≤baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue KISQALI.	Discontinue KISQALI
Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline grade, discontinue KISQALI.			

Liver Function Tests (LFTs) should be performed before initiating treatment with KISQALI.

After initiating treatment with KISQALI, LFTs should be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

If Grade 2, 3 or 4 abnormalities are noted, more frequent monitoring is recommended.

ULN = upper limit of normal

*****Baseline = prior to treatment initiation. Grading according to CTCAE Version 4.0. CTCAE=Common Terminology Criteria for Adverse Events

Table 5 Dose modification and management for other toxicities*

	Grade 1 or 2	Grade 3	Grade 4
Other toxicities	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1 resume KISQALI at same dose level. If grade 3 recurs, resume KISQALI at the next lower dose level.	Discontinue KISQALI.

*****excluding neutropenia, febrile neutropenia, hepatobiliary toxicity, and QT interval prolongation.

Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.

Dose modification for use of KISQALI with strong CYP3A inhibitors

Avoid concomitant use of KISQALI with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, reduce the KISQALI dose to 200 mg once daily.

Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring of signs of toxicity is recommended. If the strong inhibitor is discontinued, the KISQALI dose should be changed (after 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see sections 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicines and other forms of interactions, and 5.2 Pharmacokinetic properties).

Special populations

Renal impairment
Based on population pharmacokinetic analyses, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2 Pharmacokinetic properties). There is limited experience in patients with moderate renal impairment and no experience in patients with severe renal failure or who require haemodialysis with the use of KISQALI. Caution and close monitoring for toxicity should be used in patients with severe renal impairment. Based on a renal impairment study in non-cancer subjects, the recommended starting dose is 200 mg KISQALI once daily for patients with severe renal impairment (see section 5.2 Pharmacokinetic properties).

Hepatic impairment
A pharmacokinetic study in healthy subjects and non-cancer subjects with impaired hepatic function found that no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A dose adjustment is required in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) can have increased (less than 2-fold) exposure to ribociclib, and the starting dose of Kisqali 400 mg once daily is recommended. Ribociclib has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section 5.2 Pharmacokinetic properties).

Review the full Product Information for co-administered medicines (aromatase inhibitor, fulvestrant, or LHRH agonist) for dose modifications related to hepatic impairment.

Paediatric use
The safety and efficacy of KISQALI in children and adolescents aged below 18 years have not been established.

Use in the elderly
No dose adjustment is necessary (see section 5.2 Pharmacokinetic properties).

Administration
KISQALI should be administered orally once daily at the same time every day, preferably in the morning, with or without food.

If the patient vomits after taking the 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.

KISQALI tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

4.3 Contraindications

KISQALI is contraindicated in patients with corrected QT interval (QTcF) >450 milliseconds (ms) prior to treatment, or who have long QT syndrome, or who are at significant risk of developing QTc prolongation (see section 4.4 Special warnings and precautions for use).

KISQALI is contraindicated in patients with hypersensitivity to ribociclib succinate or any of the excipients, which include soya lecithin (see section 6.1 List of Excipients).

4.4 Special warnings and precautions for use

QT interval prolongation

KISQALI causes QT interval prolongation in a concentration-dependent manner (see section 5.1 Pharmacological properties - Cardiac electrophysiology).

Increased QT prolongation occurs with co-administration of KISQALI and tamoxifen. Use of KISQALI with tamoxifen is not recommended (see sections 4.8 Adverse effects (undesirable effects) and 5.1 Pharmacological properties - Cardiac electrophysiology).

The phase III clinical studies (MONALEESA-2, MONALEESA-7 and MONALEESA-3) excluded patients with certain conditions known to increase QT prolongation risk, such as heart failure, cardiomyopathy, or recent coronary disease. Across these studies, in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (1%) had >500 ms post-baseline QTcF value, and 59 out of 1054 patients (6%) had a >60 ms increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and the majority (63%) occurred within the first four weeks of treatment. There were no reported cases of *Torsades de Pointes*.

In MONALEESA-2, in the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalaemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 (see section 4.8 Adverse effects (undesirable effects)).

ECG should be assessed before initiating treatment. Treatment with KISQALI should be initiated only in patients with QTcF values <450 ms (see section 4.3 Contraindications). ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. More intensive ECGs should be considered based on a patient's individual risk factors, if there are any symptoms that may be related to QT prolongation (e.g. palpitations or syncope), or if there is any increase in the risk of QT prolongation (e.g. new medication, or condition that may increase the likely exposure to ribociclib).

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be performed before initiating treatment, at the beginning of each of the first 6 cycles, and then as clinically indicated. Treatment should be interrupted for any abnormalities to be corrected before commencing or continuing KISQALI therapy.

KISQALI should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients with:

- QTcF >450 ms prior to treatment (see section 4.3 Contraindications)
- a history of ventricular arrhythmias
- long QT syndrome
- significant risk of developing QTc prolongation including:
    - uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
    - electrolyte abnormalities

KISQALI should be avoided in patients taking medicinal products that are known to prolong the QTc interval (see section 4.5 Interactions with other medicines and other forms of interactions) and/or strong CYP3A inhibitors as this may lead to clinically meaningful prolongation of the QTcF interval. If treatment with a strong CYP3A4 inhibitor cannot be

avoided, the dose should be reduced to 200 mg once daily (see section 4.2 Dose and method of administration, section 4.5 Interactions with other medicines and other forms of interactions, and section 5.2 Pharmacokinetic properties).

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 2 (see sections 4.2 Dose and method of administration, 4.8 Adverse effects (undesirable effects) and 5.2 Pharmacological properties).

Hepatobiliary toxicity

Ribociclib commonly causes reversible elevations in transaminase levels, and uncommonly causes life-threatening hepatotoxicity.

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Grade 3 or Grade 4 increases in ALT (10% vs 2%) and AST (7% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade 3 or Grade 4 ALT/AST elevation, the median time to onset was 85 days for patients treated with KISQALI plus an aromatase inhibitor or fulvestrant. The median time to resolution (to normalisation or ≤Grade 2) was 22 days in patients treated with KISQALI plus an aromatase inhibitor or fulvestrant.

The majority of increases in ALT and AST were reported without concurrent elevation of bilirubin. In MONALEESA-2 and MONALEESA-3, concurrent elevations of ALT or AST greater than three times the upper limit of normal (ULN) and of total bilirubin greater than two times the ULN, with normal alkaline phosphatase levels, in the absence of cholestasis occurred in 6 patients (1%), and all patients recovered after discontinuation of KISQALI. There were no such cases in MONALEESA-7.

Liver function tests (LFTs) should be performed before initiating therapy with KISQALI. LFTs should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and then as clinically indicated.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 4 (see section 4.2 Dose and method of administration). Recommendations for patients who have elevated AST/ALT >Grade 3 at baseline have not been established.

Neutropenia

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (74%) and a Grade 3 or Grade 4 decrease in neutrophil counts (based on laboratory findings) was reported in 59% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grades 2, 3 or 4 neutropenia, the median time to onset was 16 days. The median time to resolution of Grade ≥3 neutropenia (to normalisation or Grade <3) was 12 days in patients treated with KISQALI plus an aromatase inhibitor or fulvestrant. Febrile neutropenia was reported in 1% of patients exposed to KISQALI plus an aromatase inhibitor or fulvestrant. Patients should be instructed to report any fever promptly (see section 4.8 Adverse effects (undesirable effects)).

A Full Blood Count (FBC) should be performed before initiating therapy with KISQALI. FBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and then as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 3 (see section 4.2 Dose and method of administration).

Reproductive toxicity and fertility

Women of reproductive potential should be advised to use an effective method of contraception while taking Kisqali and for at least 21 days after the last dose (see section 4.6 Fertility, pregnancy and lactation).

4.5 Interactions with other medicines and other forms of interactions

Drugs that may increase the QT interval

Co-administration of KISQALI with medicinal products with a known potential to prolong the QT interval may have an additive effect with ribociclib and increase the risk of QT prolongation.

Avoid co-administration of KISQALI with medicinal products with a known potential to prolong the QT interval, including, but not limited to: amiodarone, disopyramide, procainamide, quinidine, sotalol, ciprofloxacin, levofloxacin, azithromycin, moxifloxacin, erythromycin, clarithromycin, fluconazole, pentamidine, citalopram, escitalopram, lithium, clomipramine, desipramine, imipramine, trimipramine, chlorpromazine, haloperidol, ziprasidone, cisapride, ondansetron, dolasetron, chloroquine, halofantrine, methadone, bepridil, and pimozide). If co-administration cannot be avoided, consider reducing the dose of ribociclib and monitor by ECG for QT prolongation (see section 4.5 Interactions with other medicines and other forms of interactions - Drugs that may increase ribociclib plasma concentrations). KISQALI is not recommended for use in combination with tamoxifen (see section 4.4 Special warnings and precautions for use).

Interactions with co-administered anticancer medicines

Ribociclib and letrozole

Comparison of data from clinical trials in patients with breast cancer to historical controls, and a population PK analysis indicated no clinically important drug-drug interaction between ribociclib and letrozole following their co-administration.

Ribociclib and anastrozole

Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug-drug interaction between ribociclib and anastrazole following their co-administration.

Ribociclib and fulvestrant

Data from a clinical trial in patients with breast cancer indicated no clinically relevant effect of fulvestrant on ribociclib exposure following co-administration of the drugs.

Ribociclib and tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure (C_{max} and AUC) approximately doubled following co-administration of ribociclib and tamoxifen.

***In vitro* interaction data**

Effect of ribociclib on cytochrome P450 enzymes

In vitro, ribociclib is a reversible inhibitor of CYP1A2, CYP2E1 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. *In vitro* evaluations indicated that ribociclib has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. Ribociclib has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6.

In vitro data indicate that ribociclib has no potential to induce UGT enzymes or the CYP

enzymes CYP2B6, CYP2C9, CYP2C19 and CYP3A4 via CAR or PXR. Therefore, Kisqali is unlikely to affect substrates of these enzymes.

Effect of transporters on ribociclib

Based on *in vitro* data, ribociclib is a substrate of P-gp but not a substrate of BCRP. However, P-gp mediated transport is unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses because of moderate passive permeability. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro*.

Effect of ribociclib on transporters

In vitro evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters Pgp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1, MATE2K 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 digoxin, pitavastatin, pravastatin, rosuvastatin and metformin. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

Drugs that may increase ribociclib plasma concentrations

CYP3A4 inhibitors

Ribociclib is primarily metabolised by CYP3A4 and is a time-dependent inhibitor of CYP3A4 *in vitro* (see section 5.2 Pharmacokinetic properties: metabolism). Therefore, medicinal products which can influence CYP3A4 enzyme activity may alter the PK of ribociclib. No dose adjustments are required for mild and moderate CYP3A4 inhibitors, however, if treatment with a moderate CYP3A4 inhibitor is initiated, close monitoring for ribociclib-related AEs is recommended.

Concomitant use of strong CYP3A inhibitors including, but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir (see below), nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole should be avoided (see section 4.4 Special warnings and precautions for use). Alternative concomitant medications with less potential to inhibit CYP3A should be considered and patients should be monitored for adverse drug reactions (ADRs) (see section 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties: Metabolism).

If co-administration of ribociclib with a strong CYP3A inhibitor cannot be avoided, reduce KISQALI dose to 200 mg. However, there are no clinical data with this dose adjustment (see section 4.2 Dose and method of administration). If the strong inhibitor is discontinued, resume the KISQALI dose (after at least 5 half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all individual patients, therefore close monitoring for ribociclib related AEs is recommended. In case of ribociclib related toxicity, dose should be modified (see section 4.2 Dose and method of administration), or treatment should be interrupted until toxicity is resolved. (See section 4.2 Dose and method of administration, and section 5.2 Pharmacokinetic properties: Metabolism.)

Ritonavir

A drug interaction trial in healthy subjects was conducted with ritonavir (strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100 mg bid for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400 mg

ribociclib dose. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of LEE011, accounting for <10% of parent exposure) decreased by 96% and 98%, respectively.

Erythromycin

Simulations using physiologically-based pharmacokinetic modelling (PBPK) suggested that erythromycin, a moderate CYP3A4 inhibitor, may increase ribociclib C_{max} and AUC by 1.3-fold and 1.9-fold, respectively.

Drugs that may decrease ribociclib plasma concentrations

CYP3A4 inducers

Avoid concomitant use of strong CYP3A inducers including, but not limited to, phenytoin, rifampin, carbamazepine and St John's Wort *(Hypericum perforatum)*. Consider an alternate concomitant medication with no or minimal potential to induce CYP3A (see section 4.4 Special warnings and precautions for use).

Rifampicin

A drug interaction trial in healthy subjects was conducted with rifampicin, a strong CYP3A4 inducer. Compared to ribociclib alone, co-administration with rifampicin (600 mg daily for 14 days) decreased ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively.

Efavirenz

Simulations using PBPK suggested that efavirenz, a moderate CYP3A inducer, may decrease ribociclib C_{max} and AUC by 37% and 60%, respectively.

Effect of ribociclib on other drugs

CYP3A substrates

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.

Caution is recommended in case of concomitant use with sensitive CYP3A substrates with a narrow therapeutic index (see section 4.4 Special warnings and precautions for use). The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

Midazolam

Simulations using PBPK suggested that at a 600 mg ribociclib dose, midazolam C_{max} and AUC may increase 2.4-fold and 5.2-fold, respectively.

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of ribociclib (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based PK (PBPK) models suggested that ribociclib given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold.

Caffeine

Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600 mg ribociclib dose.

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of ribociclib (400 mg)

decreased C_{max} by 10% and increased the caffeine AUC_{inf} by 20% in healthy subjects, compared with administration of caffeine alone. At the clinically relevant ribociclib dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (less than 2-fold increase in AUC).

Drug-food interactions

Patients should be instructed to avoid fruits (including fruit juices) that are known to be strong inducers or inhibitors of cytochrome CYP3A enzymes and may therefore increase exposure to ribociclib. These include grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.

KISQALI can be administered with or without food (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Gastric pH elevating medications

Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption with proton pump inhibitors was not observed in population pharmacokinetic analysis, non–compartmental pharmacokinetic analyses nor in simulations using PBPK models.

4.6 Fertility, pregnancy, and lactation

Effects on Fertility

There are no clinical data available regarding effects of KISQALI on human fertility. Based on animal studies, KISQALI may impair fertility in males of reproductive potential.

Use in Pregnancy (Category D)

There are no adequate and well-controlled studies in pregnant women. Based on findings in animals, ribociclib can cause foetal harm (including fetal developmental abnormalities and fetal loss) when administered to a pregnant woman (see section 5.3 Preclinical safety data). KISQALI is not recommended during pregnancy and in females of reproductive potential not using highly effective contraception.

Pregnancy testing

The pregnancy status for females of reproductive potential should be verified prior to initiating treatment with KISQALI.

Contraception

Females of reproductive potential who are receiving KISQALI should use effective contraception (methods that result in less than 1 % pregnancy rates) during therapy and for at least 21 days after stopping treatment with KISQALI.

Use in Lactation

It is not known if KISQALI is present in human milk. There are no data on the effects of KISQALI on the breastfed child or the effects of KISQALI on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats (see section 5.3 Preclinical safety data). Patients receiving KISQALI should not breastfeed for at least 21 days after the last dose.

4.7 Effects on ability to drive and use machines

No studies on the effects of ribociclib on the ability to drive or operate machinery have been conducted. Patients experiencing fatigue, dizziness, or vertigo while taking ribociclib should exercise caution when driving or operating machinery (see section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

Clinical trial data

MONALEESA-2: KISQALI in combination with letrozole

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

The safety data reported below are based on a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥12 months. Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Among patients receiving KISQALI plus letrozole, 7% were reported to have permanently discontinued both KISQALI and letrozole and 7% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus letrozole, 2% were reported to have permanently discontinued both and 0.9% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), vomiting (2%). Antiemetics and antidiarrhoea medications were used to manage symptoms as clinically indicated.

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

The most common ARs (reported at a frequency ≥20% in the KISQALI arm and ≥2% higher than placebo) were neutropenia, nausea, fatigue, diarrhoea, leukopenia, alopecia, vomiting, constipation, headache, and back pain.

ARs and laboratory abnormalities occurring in patients in MONALEESA-2 are listed in Table 6 and Table 7, respectively. The most common Grade 3/4 ARs (reported at a frequency ≥5%) were neutropenia, leukopenia, abnormal liver function tests, and lymphopenia. Syncope occurred in 9 patients (3%) in the KISQALI plus letrozole arm versus 3 (1%) in the placebo plus letrozole arm.

Table 6 Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in MONALEESA-2 (all grades at first interim analysis)

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

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

Table 7 Laboratory abnormalities occurring ≥10 % of patients in MONALEESA-2 at first interim analysis

	KISQALI + letrozole N = 334			Placebo + letrozole N = 330		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Haematology						
Leukocyte count decreased	93	31	3	29	1	< 1
Neutrophil count decreased	93	49	11	24	1	< 1
Haemoglobin decreased	57	2	0	26	1	0
Lymphocyte count decreased	51	12	2	22	3	1
Platelet count decreased	29	1	< 1	6	0	< 1
Chemistry						
Alanine aminotransferase increased	46	8	2	36	1	0
Aspartate aminotransferase increased	44	6	1	32	2	0
Creatinine increased	20	1	0	6	0	0
Phosphorous decreased	13	5	1	4	1	0
Potassium decreased	11	1	1	7	1	0

MONALEESA-7: KISQALI in combination with an aromatase inhibitor

Pre- or perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy

MONALEESA-7 was conducted in 672 pre- or perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus endocrine therapy (goserelin plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen) or placebo plus endocrine therapy (goserelin plus either a NSAI or tamoxifen). The median duration of exposure on the KISQALI arm was 15.2 months with 66% of patients exposed for ≥12 months.

KISQALI is not recommended for use in combination with tamoxifen due to the risk of QTc prolongation (see Section 4.4 Special warnings and precautions for use).

The safety data reported below are based on 495 NSAI-treated patients, which included 248 patients who received KISQALI plus goserelin plus NSAI (the KISQALI arm) and 247 patients who received placebo plus goserelin plus NSAI (the placebo arm). Dose reductions due to adverse reactions (ARs) occurred in 33% of patients in the KISQALI arm and in 4% of patients in the placebo arm. In the KISQALI arm, 3% were reported to have permanently discontinued both KISQALI and NSAI and 3% were reported to have permanently discontinued KISQALI alone due to ARs. In the placebo arm, 2% were reported to have permanently discontinued both and 0.8% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to KISQALI or placebo treatment discontinuation in the KISQALI arm versus the placebo arm were ALT increased (2% vs 0.8%), AST increased (2% vs 0.8%) and drug-induced liver injury (1% vs 0.4%).

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-7 are listed in Table 8 and Table 9, respectively. The most common ARs (reported at a frequency ≥20% in the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, arthralgia, nausea, and alopecia. The most common Grade 3/4 ARs (reported at a frequency ≥5%) were neutropenia, leukopenia, and abnormal liver function tests.

Table 8 Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in MONALEESA-7 (NSAI-treated patients only) (all grades)

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Infections[1]	35	2	0	24	< 1	0
Blood and lymphatic system disorders						
Neutropenia	78	55	10	7	2	< 1
Leukopenia	29	13	< 1	3	< 1	0
Anaemia	19	3	0	8	1	0
Respiratory, thoracic and mediastinal disorders						
Cough	15	0	0	10	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	33	< 1	0	29	1	0
Gastrointestinal disorders						
Nausea	31	0	0	20	0	0
Constipation	16	0	0	12	0	0
Stomatitis	10	0	0	8	< 1	0
Skin and subcutaneous tissue disorders						
Alopecia	21	0	0	13	0	0
Rash	17	< 1	0	9	0	0
Pruritus	10	0	0	4	0	0
General disorders and administration site conditions						
Pyrexia	17	< 1	0	6	0	0
Pain in extremity	10	0	0	8	1	0
Investigations						
Alanine aminotransferase increased	13	5	0	9	1	0
Aspartate aminotransferase increased	13	4	0	10	1	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%).

Table 9 Laboratory abnormalities occurring in ≥10% of patients in MONALEESA-7

	KISQALI + NSAI + goserelin N = 248			Placebo + NSAI + goserelin N = 247		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Haematology						
Leukocyte count decreased	93	34	2	30	< 1	< 1
Neutrophil count decreased	92	54	9	27	2	0
Haemoglobin decreased	84	2	0	51	< 1	0
Lymphocyte count decreased	55	12	2	18	2	< 1
Platelet count decreased	26	< 1	0	9	0	< 1
Chemistry						
Alanine aminotransferase increased	33	6	0	31	1	< 1
Aspartate aminotransferase increased	37	5	0	35	1	< 1
Creatinine increased	21	2	< 1	20	< 1	< 1
Phosphorous decreased	14	2	0	11	< 1	< 1
Potassium decreased	11	< 1	< 1	14	< 1	< 1
Gamma-glutamyl transferase increased	42	5	2	42	8	1
Glucose serum decreased	10	< 1	0	10	< 1	0

MONALEESA-3: KISQALI in combination with fulvestrant

Postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy or after disease progression on endocrine therapy

The safety data reported below are based on a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥12 months. Dose reductions due to adverse reactions (ARs) occurred in 32% of patients receiving KISQALI plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Among patients receiving KISQALI plus fulvestrant, 8% were reported to have permanently discontinued both KISQALI and fulvestrant and 9% were reported to have discontinued KISQALI alone due to ARs. Among patients receiving placebo plus fulvestrant, 4% were reported to have permanently discontinued both and 2% were reported to have discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus fulvestrant (as compared to the placebo arm) were ALT increased (5% vs 0%), AST increased (3% vs 0.6%), and vomiting (1% vs 0%).

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 10 and Table 11 respectively. The most common ARs (reported at a frequency ≥20% in the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhoea, vomiting, constipation, pruritus, and rash. The most common Grade 3/4 ARs (reported at a frequency ≥5%) were neutropenia, leukopenia, infections, and abnormal liver function tests.

Table 10 Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in MONALEESA-3 (all grades)

	KISQALI + fulvestrant N = 483			Placebo + fulvestrant N = 241		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Infections[1]	42	5	0	30	2	0
Blood and lymphatic system disorders						
Neutropenia	69	46	7	2	0	0
Leukopenia	27	12	< 1	< 1	0	0
Anaemia	17	3	0	5	2	0
Metabolism and nutrition disorders						
Decreased appetite	16	< 1	0	13	0	0
Nervous system disorders						
Dizziness	13	< 1	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	22	0	0	15	0	0
Dyspnoea	15	1	< 1	12	2	0
Gastrointestinal disorders						
Nausea	45	1	0	28	< 1	0
Diarrhoea	29	< 1	0	20	< 1	0
Vomiting	27	1	0	13	0	0
Constipation	25	< 1	0	12	0	0
Abdominal pain	17	1	0	13	< 1	0
Skin and subcutaneous tissue disorders						
Alopecia	19	0	0	5	0	0
Pruritus	20	< 1	0	7	0	0
Rash	23	< 1	0	7	0	0
General disorders and administration site conditions						
Oedema peripheral	15	0	0	7	0	0
Pyrexia	11	< 1	0	7	0	0
Investigations						
Alanine aminotransferase increased	15	7	2	5	< 1	0
Aspartate aminotransferase increased	13	5	1	5	< 1	0

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

[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (< 1%).

Table 11 Laboratory abnormalities occurring in ≥10% of patients in MONALEESA-3	KISQALI + fulvestrant			Placebo + fulvestrant		
		N = 483			N = 241	
Laboratory parameters	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematology						
Leukocyte count decreased	95	25	< 1	26	< 1	0
Neutrophil count decreased	92	46	7	21	< 1	0
Haemoglobin decreased	60	4	0	35	3	0
Lymphocyte count decreased	69	14	1	35	4	< 1
Platelet count decreased	33	< 1	1	11	0	0
Chemistry						
Creatinine increased	65	< 1	< 1	33	< 1	0
Gamma-glutamyl transferase increased	52	6	1	49	8	2
Aspartate aminotransferase increased	49	5	2	43	3	0
Alanine aminotransferase increased	44	8	3	37	2	0
Glucose serum decreased	23	0	0	18	0	0
Phosphorous decreased	18	5	0	8	< 1	0
Albumin decreased	12	0	0	8	0	0

Description of selected adverse drug reactions

QT prolongation

In the phase III clinical studies, 8% of ribociclib-treated patients and 3% of placebo-treated patients had at least one event of QT interval prolongation or syncope. Dose interruptions/adjustments were reported in 2% of the KISQALI-treated patients due to QT interval prolongation or syncope.

A central analysis of ECG data (average of triplicate) showed that at least one post-baseline QTcF of >480 ms occurred in 5% ribociclib-treated patients and 1% of placebo-treated patients. Among the ribociclib-treated patients who had QTcF prolongation of >480 ms, the median time to onset was 15 days regardless of what treatment ribociclib was combined with, and these changes were reversible with dose interruption and/or dose reduction (see section 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties).

In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen plus placebo subgroup compared with NSAI plus placebo subgroup, suggesting that tamoxifen contributed to the QTcF prolongation observed in the ribociclib plus tamoxifen group (see section 5.1 Pharmacological properties - Cardiac electrophysiology). A QTcF increase of >60 ms from baseline occurred in zero patients who received placebo plus NSAI, 7% of patients who received placebo plus tamoxifen, 7% of patients who received ribociclib plus NSAI, and 16% of patients who received ribociclib plus tamoxifen. Co-administration of

KISQALI and tamoxifen is not recommended (see section 4.4 Special warnings and precautions for use).

Hepatobiliary toxicity

Across the phase III clinical studies, hepatobiliary toxicity events occurred in a higher proportion of ribociclib–treated patients compared with placebo-treated patients (23% vs 17%), and more Grade 3/4 adverse events were reported in ribociclib-treated than placebo-treated patients (11% vs 5%). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 10% of ribociclib-treated patients, primarily due to ALT increased (7%) and/or AST increased (6%). Discontinuation of treatment with KISQALI due to abnormal liver function tests and hepatotoxicity occurred at rates of 2% and 0.4% respectively (see section 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties).

Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III studies Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Permanent treatment discontinuation due to neutropenia was low in patients receiving KISQALI (0.8%), however, dose interruptions and/or modifications were required in around half of ribociclib-treated patients (see section 4.2 Dose and method of administration, and section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdosage

Symptoms and Signs

Limited experience in humans suggests that in the event of KISQALI overdosage, nausea, vomiting, neutropenia and thrombocytopenia could occur. QTc prolongation may also occur, as it is known to be concentration-dependent.

Treatment

The treatment of overdose should consist of general symptomatic and supportive measures. For information on the management of overdose, contact the Poison Information Centre on telephone number 13 11 26 (local call in all areas).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors

Anatomical Therapeutic Chemical (ATC) code: L01XE42

Mechanism of action

Ribociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signalling pathways which lead

to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

In vitro, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. In vivo, treatment with single agent ribociclib in a rat xenograft model with human tumour cells led to decreased tumour volumes, which correlated with inhibition of pRb phosphorylation.

In studies using patient-derived oestrogen receptor-positive breast cancer xenograft models, combination of ribociclib and antioestrogen (e.g. letrozole) resulted in increased tumour growth inhibition compared to each drug alone. Additionally, the combination of ribociclib and fulvestrant resulted in tumor growth inhibition in an estrogen receptor positive breast cancer xenograft model.

Pharmacodynamic effects

Ribociclib inhibits the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (IC_{50}) values of 0.01 micromolar (μM) (4.3 ng/mL) and 0.039 μM (16.9 ng/mL) in biochemical assays, respectively.

In cell based assays with pRb positive cancer cell lines, ribociclib inhibits CDK4/6-dependent pRb phosphorylation with an IC_{50} of 0.06 μM (26 ng/mL). Ribociclib halts G1 to S-phase cell cycle progression measured by flow cytometry with IC_{50} of 0.11 μM (47.8 ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine uptake with IC_{50} of 0.08-μM (34.8 ng/mL).

When tested in a panel of breast cancer cell lines with known ER status, ER-positive cell lines were more sensitive than ER-negative cell lines to the anti-proliferation effects of ribociclib. Ribociclib had no inhibitory activity in the tested pRb-negative cancer cell lines.

Cardiac electrophysiology

Serial, triplicate electrocardiograms (ECGs) were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. *In vitro* studies have shown that both ribociclib and its major metabolite, LEQ803, interact with hERG channels. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 mg to 1200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF for KISQALI 600 mg in combination with aromatase inhibitors or fulvestrant was 22.0 ms (90% CI: 20.6, 23) and 23.7 ms (90% CI: 22.3, 25.1), respectively, and was 34.7 ms (90% CI: 31.6, 37.8) in combination with tamoxifen at the geometric mean C_{max} at steady-state (see section 4.4 Special warnings and precautions for use).

Clinical trials

MONALEESA 2

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

A total of 668 patients were randomised to receive either KISQALI plus letrozole (n= 334) or placebo plus letrozole (n=334), stratified according to the presence of liver and/or lung metastases. Demographics and baseline disease characteristics were balanced and comparable between study arms. Letrozole 2.5 mg was given orally once daily for 28 days, with either KISQALI 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days

off treatment, until disease progression or unacceptable toxicity. Patients who had prior neoadjuvant or adjuvant therapy with anastrozole or letrozole must have completed it at least 12 months before study randomisation, and patients were not allowed to cross over from placebo to KISQALI during the study or after disease progression. The primary efficacy endpoint for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients enrolled in MONALEESA-2 had a median age of 62 years (range 23 to 91). The majority of patients were Caucasian (82%), Asian (8%) or Black (3%),and all patients had an ECOG performance status of 0 or 1. A total of 44% of patients had received chemotherapy and 52% had received antihormonal therapy in the neoadjuvant or adjuvant setting. At study entry, 34% of patients had *de novo* metastatic disease, 21% had bone only disease and 59% had visceral disease.

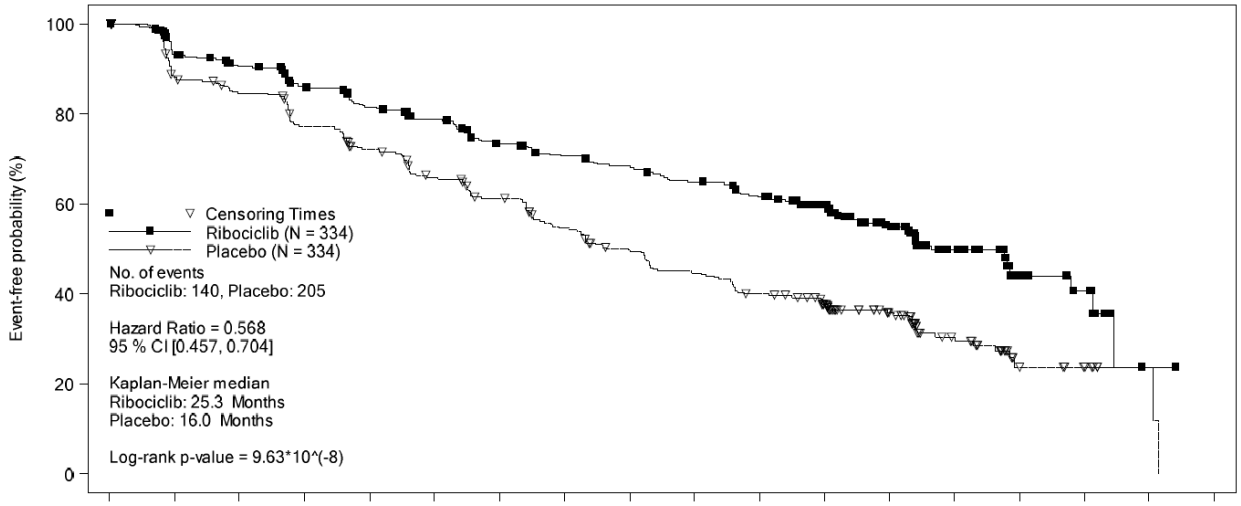
The efficacy findings are summarised in Table 12 and Figure 1. The results shown are from pre-planned primary interim efficacy analysis of PFS and from an updated analysis performed at the time of the second interim analysis of overall survival (OS). Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment. At the time of the second interim OS analysis, 17% of patients had died, and OS data remained immature.

Table 12 Efficacy results from MONALEESA 2 (investigator-assessed, intent-to-treat (ITT) population)

	First interim analysis (29 Jan 2016 data cut-off)[a]		**Updated analysis** (2 Jan 2017 data cut-off)[b]	
	KISQALI plus letrozole n=334	**Placebo plus letrozole n=334**	**KISQALI plus letrozole n=334**	**Placebo plus letrozole n=334**
Progression-free survival (PFS)				
Number of events, n (%)	93 (27.8)	150 (44.9)	140 (41.9)	205 (61.4)
Median PFS [months] (95% CI)	NE (19.3, NE)	14.7 (13.0, 16.5)	25.3 (23.0, 30.3)	16.0 (13.4,18.2)
Hazard ratio (95% CI)	0.556 (0.429, 0.720)		0.568 (0.457, 0.704)	
p-value[c]	0.00000329		0.0000000963	
Patients with measurable disease	**n=256**	**n=245**	**n=257**	**n=245**
Overall Response Rate[b] (ORR) (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)	54.5 (48.4, 60.6)	38.8 (32.7, 44.9)

CI = confidence interval; n = number of patients; NE = not estimable
[a] Median duration of study follow up = 15.3 months
[b] Median duration of study follow up = 26.4 months
[c] p-value is obtained from the one-sided stratified log-rank test [b] ORR: Overall Response Rate = proportion of patients with complete response + partial response;

Figure 1 Kaplan-Meier curve for PFS (investigator-assessed, ITT population, 2 Jan 2017 data cut-off)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Ribociclib	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
Placebo	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

CI Confidence interval; PFS Progression-free survival

MONALEESA-7

MONALEESA-7 was a randomised, double-blind, placebo-controlled, multicentre clinical study of KISQALI plus endocrine therapy (goserelin plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen) versus placebo plus endocrine therapy (goserelin plus either a NSAI or tamoxifen) for the treatment of pre- and perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who had received no prior endocrine therapy for advanced disease.

A total of 672 patients were randomised to receive either KISQALI plus goserelin plus NSAI/tamoxifen (n=335) or placebo plus goserelin plus NSAI/tamoxifen (n=337), stratified according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease and endocrine combination partners (NSAI and goserelin [n=493] versus tamoxifen and goserelin [n=179]). KISQALI is not recommended for use in combination with tamoxifen due to the risk of QTc prolongation (see Section 4.4 Special warnings and precautions for use).

In the NSAI-treated patients, NSAI (letrozole 2.5 mg or anastrozole 1 mg) was given orally once daily on a continuous schedule, and goserelin (3.6 mg) was administered subcutaneously on day 1 of each 28 day cycle, with either KISQALI 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to KISQALI during the study or after disease progression, or to switch between endocrine combination partners. The primary efficacy endpoint for the study was investigator-assessed PFS using RECIST v1.1.

Patients enrolled in MONALEESA-7 had a median age of 44 years (range 25 to 58) and 28% were younger than 40. The majority of patients were Caucasian (58%), Asian (29%) or Black (3%), and nearly all patients (99%) had an ECOG performance status of 0 or 1. Of the 672 patients, 14% had received prior chemotherapy for metastatic disease, 33% had received chemotherapy in the adjuvant setting, 18% had received chemotherapy in the neoadjuvant setting, 40% had received endocrine therapy in the adjuvant setting, and 0.7% had received

endocrine therapy in the neoadjuvant setting. At study entry, 40% of patients had de novo metastatic disease, 24% had bone only disease, and 57% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms, including in endocrine combination partner subgroups.

The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KISQALI or placebo in combination with NSAI plus goserelin are summarised in Table 13 and Figure 5. In the NSAI subgroups, there was no significant difference demonstrated between the treatment arms for the Time to response (TTR) or Duration of response (DoR) – responders. Consistent results were observed in stratification subgroups of disease site and prior chemotherapy for advanced disease. At the time of the PFS analysis, 13% of patients had died, and overall survival data were immature.

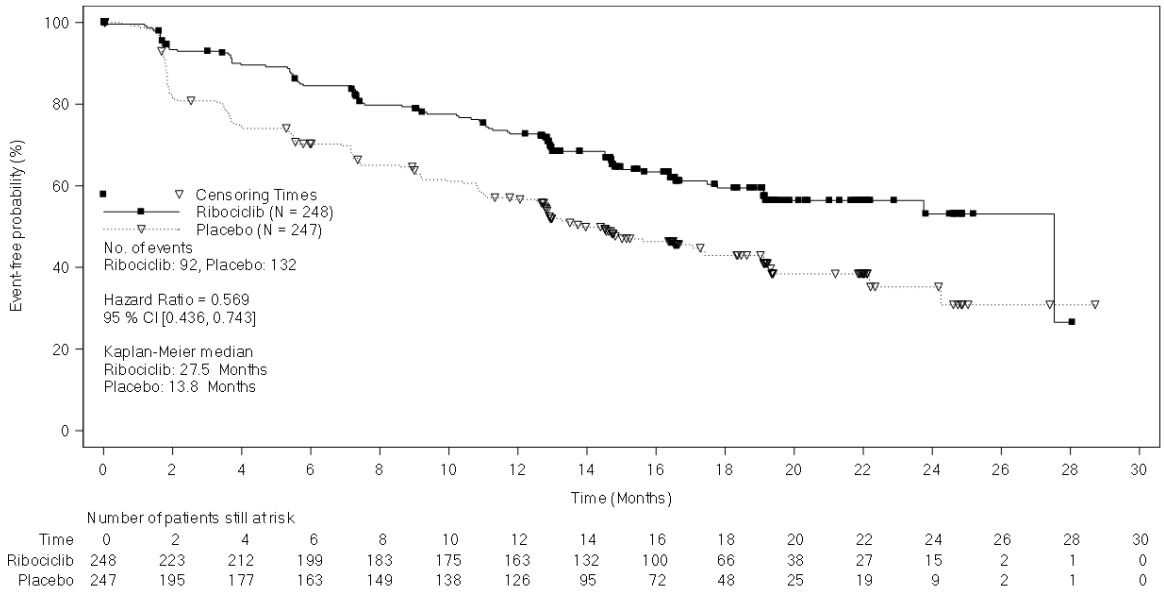
Table 13 Efficacy results from MONALEESA-7 (investigator-assessed, NSAI subgroup)

	KISQALI + NSAI + goserelin	Placebo + NSAI + goserelin
Progression free survival (PFS)	**N=248**	**N=247**
Median PFS [months] (95% CI)	27.5 (19.1, NE)	13.8 (12.6, 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	
Patients with measurable disease	**N=192**	**N=199**
Overall response rate (ORR) [a] 95% CI	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)

CI = confidence interval; N = number of patients; NE = not estimable.

[a] *Based on confirmed responses ORR: Overall Response Rate = proportion of patients with complete response + partial response,*

Figure 2 Kaplan-Meier curve for PFS from MONALEESA-7 (investigator-assessed, NSAI subgroup)



MONALEESA-3

MONALEESA-3 was a randomised double-blind, placebo-controlled, multicentre clinical study of KISQALI plus fulvestrant versus placebo plus fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who had received no or only one line of prior endocrine treatment for advanced disease.

A total of 726 patients were randomised to receive either KISQALI plus fulvestrant (n=484) or placebo plus fulvestrant (n=242), stratified according to the presence of liver and/or lung metastases and prior endocrine therapy. Fulvestrant 500 mg was administered intramuscularly on days 1, 15, 29, and once monthly thereafter, with either KISQALI 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The primary efficacy endpoint for the study was investigator-assessed PFS using RECIST v1.1.

Patients enrolled in MONALEESA-3 had a median age of 63 years (range 31 to 89), and 14% were at least 75 years old. The majority of patients were Caucasian (85%), Asian (9%) or Black (1%), and nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of which 19% had *de novo* metastatic disease). Of the 726 patients, 43% had received chemotherapy in the adjuvant setting, 13% had received chemotherapy in the neoadjuvant setting, 59% had received endocrine therapy in the adjuvant setting and 1% had received endocrine therapy in the neoadjuvant setting. At study entry, 21% of patients had bone only disease and 61% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

The efficacy results from MONALEESA-3 are summarised in Table 14 and Figure 6. Consistent results were observed in stratification subgroups of disease site and prior endocrine treatment for advanced disease.

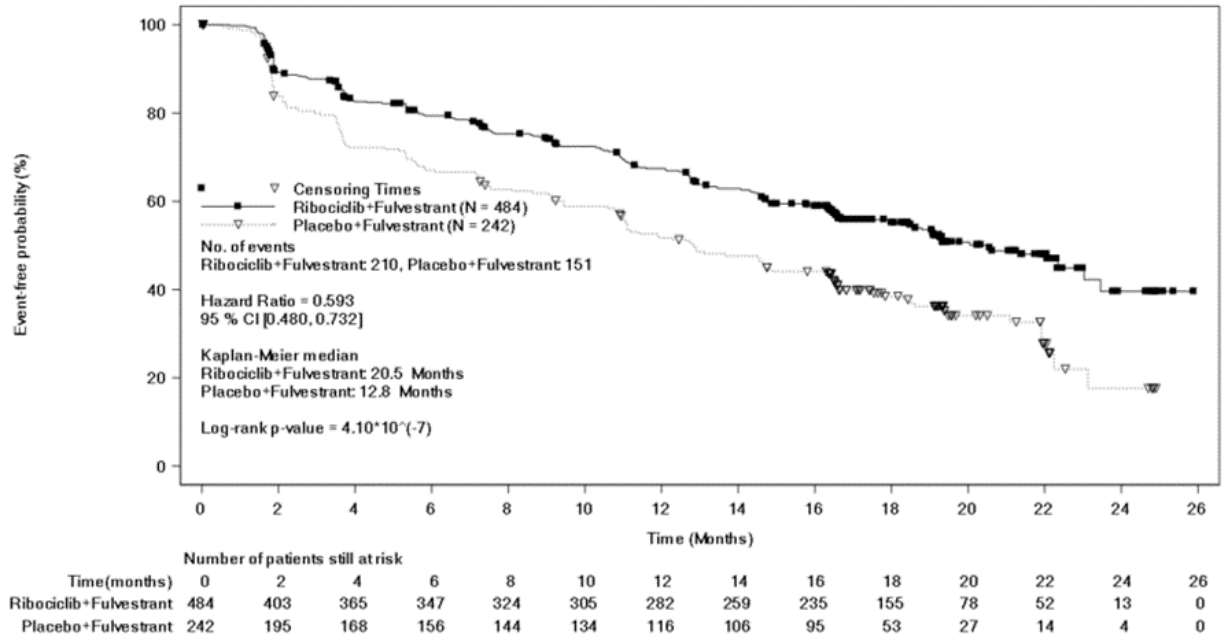
At the time of the PFS analysis, 17% of patients had died, and overall survival data were immature.

Table 14 Efficacy results from MONALEESA-3 (investigator-assessed, ITT population)

	KISQALI + fulvestrant	**Placebo + fulvestrant**
Progression free survival	**N=484**	**N=242**
Median PFS [months] (95% CI)	20.5 (18.5 – 23.5)	12.8 (10.9 – 16.3)
Hazard ratio (95% CI)	0.593 (0.480 - 0.732)	
p-value[a]	0.00000041	
Patients with measurable disease	**N=379**	**N=181**
Overall response rate (ORR)[b]	40.9 (35.9 , 45.8)	28.7 (22.1, 35.3)
Time to response (TTR)	**N=484**	**N=282**
Median TTR [months] (95% CI)	NE (NE , NE)	NE (NE , NE)
Probability of response by 6 months	26.6 (22.7, 31.0)	16.2 (12.0, 21.6)

CI = confidence interval; N = number of patients; NE = not estimable.
[a] p-value is obtained from the one-sided stratified log-rank test
[B] Based on confirmed responses, ORR: Overall Response Rate = proportion of patients with complete response + partial response

Figure 3 Kaplan-Meier curve for PFS from MONALEESA-3 (investigator-assessed, ITT population)



5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of ribociclib was investigated in patients with advanced cancer following oral daily doses ranging from 50 mg to 1200 mg. Healthy subjects received single oral doses ranging from 400 mg to 600 mg or repeated daily oral doses (for 8 days) at 400 mg. At the recommended dose of ribociclib 600 mg, the inter-patient variability in pharmacokinetics was approximately 60%.

Absorption

Following oral administration of KISQALI to patients with advanced solid tumours or lymphomas, peak plasma levels (C_{max}) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T_{max}). Following repeated once daily dosing, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.97 to 6.40).

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. The observed over-proportional increases in exposure might be attributed to auto-inhibition of CYP3A4. This analysis is limited by the small sample sizes for most of the dose cohorts with the majority of data coming from the 600 mg dose cohort.

Food effect

Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib. The geometric mean ratio (GMR) for C_{max} was 1.00 (90% CI: 0.898, 1.11) and for AUC_{inf} was 1.06 (90% CI: 1.01, 1.12).

See also fruits and juices to avoid in section 4.5 Interactions with other medicines and other forms of interactions.

Distribution

Binding of ribociclib to human plasma proteins in vitro was approximately 70% and independent of concentration (10 ng/mL to 10000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.04. The mean apparent volume of distribution at steady-state (Vss/F) was 1090 L based on population PK analysis.

Metabolism

In vitro and *in vivo* studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [^{14}C] ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation {dealkylation, C and/or N-oxygenation, oxidation (-2H)} and combinations thereof. Phase II conjugates of ribociclib Phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure respectively. Clinical activity (pharmacological and safety) of ribociclib was due primarily to the parent drug, with negligible contribution from the circulating metabolites.

Ribociclib was extensively metabolised with unchanged drug accounting for 17% and 12% in faeces and urine respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in faeces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor abundance (≤3% of the administered dose).

Elimination

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

Ribociclib is eliminated mainly via faeces, with some elimination by the renal route. In six healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; faeces was the major route of excretion (69%), with 23% of the dose recovered in urine. The estimated oral absorption of ribociclib was 59%.

Special patient populations

Renal impairment

Based on a population pharmacokinetic analysis that included 438 patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2), 488 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2) and 113 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of ribociclib, no dose adjustment is necessary in patients with mild or moderate renal impairment. The pharmacokinetics of ribociclib in patients with severe renal impairment have not been studied (see section 4.2 Dose and method of administration).

The effect of renal impairment on the pharmacokinetics of ribociclib was also assessed in a renal impairment study in non-cancer subjects that included 7 subjects with normal renal

function (eGFR ≥90 mL/min/1.73 m^2), 7 subjects with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), and 3 subjects with end stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m^2) at a single ribociclib dose of 400 mg/day. In subjects with severe renal impairment AUC_{inf} increased by 2-fold, and C_{max} increased by 1.5-fold compared to subjects with normal renal function.

Based on this study, a starting dose of 200 mg is recommended for patients with severe renal impairment (see section 4.2 Dosage and method of administration).

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); a dose adjustment is required in patients with moderate (Child-Pugh B), or severe hepatic impairment (Child-Pugh C) and starting dose of 400 mg is recommended (see section 4.2 Dose and method of administration). Based on a PK trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section 4.2 Dose and method of administration). The mean exposure for ribociclib was increased less than 2-fold in patients with moderate hepatic impairment (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe hepatic impairment (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}). Based on a population PK analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section 4.2 Dose and method of administration).

Use in the elderly
Of 334 patients who received KISQALI in MONALEESA 2 (ribociclib plus letrozole arm), 150 patients (45%) were ≥65 years of age and 35 patients (10%) were ≥75 years of age. Of 484 patients who received KISQALI in MONALEESA 3 (ribociclib plus fulvestrant arm), 226 patients (47%) were ≥65 years of age and 65 patients (13%) were ≥75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients (see section 4.2 Dose and method of administration).

Paediatric use
No studies have been conducted to investigate the pharmacokinetics of ribociclib in paediatric patients.

Effect of age, weight, gender and race:
Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib that would require a dose adjustment.

5.3 Preclinical safety data

Safety pharmacology

QT prolongation

In vivo cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at an exposure that would be expected to be achieved in patients following the recommended dose of 600 mg. As well, there is potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 4-fold the anticipated clinical C_{max}).

Phototoxicity

Ribociclib was shown to absorb light in the UV-B and UV-A range, however, phototoxicity was not suggested by *in vitro* testing. The risk that KISQALI causes photosensitisation in patients is considered very low.

Repeated-dose toxicity

Repeated dose toxicity studies (treatment schedule of 3 weeks on/1 week off) in rats up to 26 weeks duration and dogs up to 39 weeks duration, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gall bladder calculi, inspissated bile, periportal hepatocyte necrosis and arteriopathy in the hilar region) as the primary target organ of toxicity of ribociclib.

Additionally, effects on bone marrow (hypocellularity), pancytopenia, lymphoid system (lymphoid depletion), testes (atrophy), intestinal mucosa (atrophy), skin (atrophy), bone/ribs (decreased bone formation), lung (increased incidence of alveolar macrophages), and kidney (concurrent degeneration and regeneration of tubular epithelial cells) were described. In general, these changes in rats and dogs demonstrated either reversibility or a clear tendency towards reversibility. Exposure to ribociclib in animals in these toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity and fertility

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in rats or rabbits. Following prenatal exposure, increased incidences of post-implantation loss and reduced foetal weights were observed in rats and ribociclib was teratogenic in rabbits at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC.

In rats, reduced foetal weights accompanied by skeletal changes considered to be transitory and/or related to the lower foetal weights were noted. In rabbits, there were adverse effects on embryo-foetal development as evidenced by increased incidences of foetal abnormalities (malformations and external, visceral and skeletal variants) and foetal growth (lower foetal weights). These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60 mg/kg), extra/rudimentary thirteenth ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-foetal mortality.

In a fertility study in female rats, ribociclib did not affect reproductive function, fertility or early embryonic development at doses up to 300 mg/kg/day (approximately 0.6 times the clinical exposure in patients at the highest recommended dose of 600 mg/day based on AUC).

Ribociclib has not been evaluated in male fertility studies. However, atrophic changes in testes were reported in rat and dog toxicity studies at exposures that were less than or equal to human exposure at the highest recommended daily dose of 600 mg/day based on AUC. These effects can be linked to a direct anti-proliferative effects on the testicular germ cells resulting in atrophy of the seminiferous tubules.

Ribociclib and its metabolites passed readily into rat milk. In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 4-fold higher in milk compared to maternal plasma.

Genotoxicity

Genotoxicity studies in bacteria, and in mammalian cells (human lymphocytes and mouse lymphoma cells) *in vitro* with and without metabolic activation, and in a micronucleus test in

rats did not reveal any evidence for a mutagenic potential of ribociclib.

Carcinogenicity

No carcinogenesis studies have been conducted with ribociclib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains microcrystalline cellulose, hyprolose, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable source), polyvinyl alcohol, titanium dioxide (E171), iron oxide black CI77499, iron oxide red CI77491, purified talc, lecithin (soya), and xanthan gum. KISQALI does not contain sucrose, lactose, gluten, or synthetic colours.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store KISQALI tablets below 30°C.

6.5 Special precautions for disposal

Any unused product should not be disposed of in household waste or wastewater. Return it to a pharmacist for safe disposal.

6.6 Nature and contents of the container

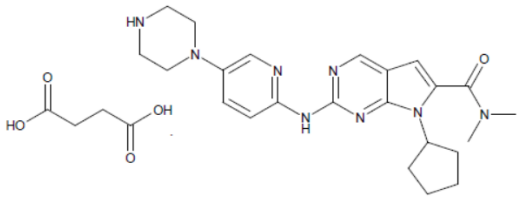
KISQALI tablets are supplied in Aclar/aluminium blisters platforms in packs containing either 63, 42, or 21 tablets.

6.7 Physicochemical properties

KISQALI tablets contain ribociclib succinate which is a light yellow to yellowish brown, crystalline powder. It is soluble in a 1:1 mixture of water and acetonitrile, and the pH of a 1% w/v aqueous solution is about 5.2 at 25°C.

Chemical name:	butanedioic acid - 7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1)
Molecular formula:	$C_{23}H_{30}N_8O.C_4H_6O_4$
Molecular weight:	As succinate: 552.64, and free base: 434.55

Chemical structure



Chemical Abstracts Service (CAS) numbers:	1374639-75-4 (as succinate) and 1211441-98-3 (as free base)

7. MEDICINE SCHEDULE (POISON SCHEDULE)

Schedule 4 – Prescription medicine

8. SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road MACQUARIE PARK NSW 2113
Telephone 1 800 671 203
Web site: www.novartis.com.au
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9. DATE OF FIRST APPROVAL

23 October 2017

10. DATE OF REVISION

12 August 2019

Summary table of changes

Section changed	Summary of new information
All	Reformatted
4.1	Revised therapeutic indication
4.2	Fulvestrant and LHRH agonist
4.4	Tamoxifen precaution, reproductive toxicity and fertility precaution, applicable MONALEESA 3 and MONALEESA 7 data
4.5	Levofloxacin, azithromycin, rosuvastatin, metformin, co-administered anticancer medicines, grapefruit hybrids, pummelos, star-fruit, and Seville oranges
4.7	Dizziness or vertigo
4.8	MONALEESA 3 and MONALEESA 7 clinical safety data
4.9	Symptoms/sign - vomiting
5.1	Data from MONALEESA 3 and MONALEESA 7 clinical studies
5.2	No pharmacokinetic data in paediatrics
5.3	Safety pharmacology

Internal document code (kis070819i)