

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Each film-coated tablet contains 0.344 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light greyish violet, unscored, round, curved with bevelled edges (approximate diameter: 11.1 mm), 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 women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

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

4.2 Posology and method of administration

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

Posology

The recommended dose is 600 mg (three 200 mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. The treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Kisqali should be used together with 2.5 mg letrozole or another aromatase inhibitor or with 500 mg fulvestrant.

When Kisqali is used in combination with an aromatase inhibitor, the aromatase inhibitor should be

taken orally once daily continuously throughout the 28-day cycle. Please refer to the Summary of Product Characteristics (SmPC) of the aromatase inhibitor for additional details.

When Kisqali is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the SmPC of fulvestrant for additional details.

Treatment of pre- and perimenopausal women with the approved Kisqali combinations should also include an LHRH agonist in accordance with local clinical practice.

Kisqali can be taken with or without food (see section 4.5). Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. 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.

Dose modifications

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction or discontinuation of Kisqali. If dose reduction is required, the recommended dose reduction guidelines are listed in Table 1.

Table 1 Recommended dose modification guidelines

	Kisqali	
	Dose	Number of 200 mg tablets
Starting dose	600 mg/day	3
First dose reduction	400 mg/day	2
Second dose reduction	200 mg*/day	1
* If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.		

Tables 2, 3, 4 and 5 summarise recommendations for dose interruption, reduction or discontinuation of Kisqali in the management of specific ADRs. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see section 4.4).

Complete blood counts (CBC) should be performed before initiating treatment with Kisqali. After initiating treatment CBC 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.

Table 2 Dose modification and management – Neutropenia

	Grade 1 or 2* (ANC 1000/mm ³ - ≤LLN)	Grade 3* (ANC 500 - <1000/mm ³)	Grade 3* febrile neutropenia**	Grade 4* (ANC <500/mm ³)
Neutropenia	No dose adjustment is required	Dose interruption until recovery to grade ≤2. Resume Kisqali at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery to grade ≤2, then resume Kisqali and reduce by 1 dose level.	Dose interruption until recovery to grade ≤2. Resume Kisqali and reduce by 1 dose level	Dose interruption until recovery to grade ≤2. Resume Kisqali and reduce by 1 dose level.
<p>* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) ** Grade 3 neutropenia with a single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection) ANC = absolute neutrophil count; LLN = lower limit of normal</p>				

Liver function tests (LFTs) should be performed before initiating treatment with Kisqali. After initiating treatment LFTs should be performed every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If grade ≥2 abnormalities are noted, more frequent monitoring is recommended.

Table 3 Dose modification and management – 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 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 of Kisqali 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.			
* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) ** Baseline = prior to treatment initiation ULN = upper limit of normal				

ECG should be assessed before initiating treatment with Kisqali. After initiating treatment, ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

Table 4 Dose modification and management – QT prolongation

ECGs with QTcF >480 msec	<ol style="list-style-type: none"> The dose should be interrupted. If QTcF prolongation resolves to <481 msec, resume treatment at the next lower dose level. If QTcF ≥481 msec recurs, interrupt dose until QTcF resolves to <481 msec and then resume Kisqali at the next lower dose level.
ECGs with QTcF >500 msec	<p>If QTcF is greater than 500 msec, interrupt Kisqali until QTcF is <481 msec then resume Kisqali at next lower dose level.</p> <p>If QTcF interval prolongation to greater than 500 msec or greater than 60 msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali.</p>

Table 5 Dose modification and management – Other toxicities*

Other toxicities	Grade 1 or 2**	Grade 3**	Grade 4**
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤ 1 , then resume Kisqali at the same dose level. If grade 3 recurs, resume Kisqali at the next lower dose level.	Discontinue Kisqali.
* Excluding neutropenia, hepatotoxicity and QT interval prolongation.			
** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)			

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

Dose modification for use of Kisqali with strong CYP3A4 inhibitors

Concomitant use of strong CYP3A4 inhibitors should be avoided and an alternative concomitant medicinal product with less potential to inhibit CYP3A4 inhibition should be considered. If patients must be given a strong CYP3A4 inhibitor concomitantly with ribociclib, the Kisqali dose should be reduced to 400 mg once daily (see section 4.5).

In patients who have had their dose reduced to 400 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 200 mg.

In patients who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, Kisqali treatment should be interrupted.

Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring of signs of toxicity is recommended. If the strong inhibitor is discontinued, the Kisqali dose should be changed to the dose used prior to the initiation of the strong CYP3A4 inhibitor after at least 5 half-lives of the strong CYP3A4 inhibitor (see sections 4.4, 4.5 and 5.2).

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2). Caution should be used in patients with severe renal impairment with close monitoring of signs of toxicity as there is no experience with Kisqali in this population (see section 5.2)

Hepatic impairment

Based on a pharmacokinetic study in healthy subjects and non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). 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 400 mg Kisqali once daily is recommended. Ribociclib has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Kisqali in children and adolescents aged below 18 years have not been established. No data are available.

Elderly

No dose adjustment is required in patients over 65 years of age (see section 5.2).

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Critical visceral disease

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

Neutropenia

Based on the severity of the neutropenia, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in Table 2 (see sections 4.2 and 4.8).

Hepatobiliary toxicity

Liver function tests should be performed before initiating treatment with Kisqali. After initiating treatment, liver function should be monitored (see sections 4.2 and 4.8).

Based on the severity of the transaminase elevations, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in Table 3 (see sections 4.2 and 4.8). Recommendations for patients who have elevated AST/ALT grade ≥ 3 at baseline have not been established.

QT interval prolongation

In study E2301 (MONALEESA-7), a QTcF interval increase >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a non-steroidal aromatase inhibitor (NSAI). Kisqali is not recommended to be used in combination with tamoxifen (see sections 4.8 and 5.1).

ECG should be assessed before initiating treatment. Treatment with Kisqali should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated (see sections 4.2 and 4.8).

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.

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

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

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 (see sections 4.2, 4.5 and 5.1). If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg once daily (see sections 4.2 and 4.5).

Based on the observed QT prolongation during treatment, treatment with Kisqali may have to be interrupted, reduced or discontinued as described in Table 4 (see sections 4.2, 4.8 and 5.2).

CYP3A4 substrates

Ribociclib is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose. Thus, ribociclib may interact with medicinal products which are metabolised via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrates (see section 4.5). 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.

Women of childbearing potential

Women of childbearing 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).

Soya lecithin

Kisqali contains soya lecithin. Patients who are hypersensitive to peanut or soya should not take Kisqali (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Substances that may increase ribociclib plasma concentrations

Ribociclib is primarily metabolised by CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of ribociclib. Co-administration of the strong CYP3A4 inhibitor ritonavir (100 mg twice daily for 14 days) with a single 400 mg dose of ribociclib increased ribociclib exposure (AUC_{inf}) and the peak concentration (C_{max}) in healthy subjects 3.2 and 1.7-fold, respectively, relative to a single 400 mg ribociclib dose given alone. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of ribociclib accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively.

The concomitant use of strong CYP3A4 inhibitors including, but not limited to, the following must be avoided: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil and voriconazole (see section 4.4). Alternative concomitant medicinal products with less potential to inhibit CYP3A4 should be considered and patients should be monitored for ribociclib-related AEs (see sections 4.2, 4.4 and 5.2).

If co-administration of Kisqali with a strong CYP3A4 inhibitor cannot be avoided, the dose of Kisqali should be reduced as described in section 4.2. However, there are no clinical data with these dose adjustments. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ribociclib-related AEs is recommended. In the event of ribociclib-related toxicity, the dose should be modified or treatment should be interrupted until toxicity is resolved (see sections 4.2 and 5.2). If the strong CYP3A4 inhibitor is discontinued, and after at least 5 half-lives of the CYP3A4 inhibitor (refer to the SmPC of the CYP3A4 inhibitor in question), Kisqali should be resumed at the same dose used prior to the initiation of the strong CYP3A4 inhibitor.

Physiologically-based pharmacokinetic simulations suggested that at a 600 mg dose of ribociclib, a moderate CYP3A4 inhibitor (erythromycin) may increase ribociclib steady-state C_{max} and AUC 1.2-fold and 1.3-fold, respectively. For patients who had their ribociclib dose reduced to 400 mg once daily, the increase of the steady-state C_{max} and AUC was estimated to be 1.4- and 2.1-fold,

respectively. The effect at the 200 mg once-daily dose was predicted to be a 1.7- and 2.8-fold increase, respectively. No dose adjustments of ribociclib are required at initiation of treatment with mild or moderate CYP3A4 inhibitors. However, monitoring of ribociclib-related AEs is recommended.

Patients should be instructed to avoid grapefruit or grapefruit juice. These are known to inhibit cytochrome CYP3A4 enzymes and may increase the exposure to ribociclib.

Substances that may decrease ribociclib plasma concentrations

Co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 14 days) with a single 600 mg dose of ribociclib decreased the ribociclib AUC_{inf} and C_{max} by 89% and 81%, respectively, relative to a single 600 mg ribociclib dose given alone in healthy subjects. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. The concomitant use of strong CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for lack of efficacy. The concomitant use of strong CYP3A4 inducers should be avoided, including, but not limited to, phenytoin, rifampicin, carbamazepine and St John's Wort (*Hypericum perforatum*). An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

The effect of a moderate CYP3A4 inducer on ribociclib exposure has not been studied. Physiologically-based pharmacokinetic simulations suggested that a moderate CYP3A4 inducer (efavirenz) may decrease steady-state ribociclib C_{max} and AUC by 51% and 70%, respectively. The concomitant use of moderate CYP3A4 inducers may therefore lead to decreased exposure and consequently a risk for impaired efficacy, in particular in patients treated with ribociclib at 400 mg or 200 mg once daily.

Substances that may have plasma concentrations altered by Kisqali

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

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kisqali (400 mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based pharmacokinetic models suggested that Kisqali given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold. Therefore, in general, when ribociclib 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 (see section 4.4). The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index, including but not limited to alfentanil, ciclosporin, everolimus, fentanyl, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

Concomitant administration of ribociclib at the 600 mg dose with the following CYP3A4 substrates should be avoided: alfuzosin, amiodarone, cisapride, pimozone, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of Kisqali (400 mg) increased the caffeine exposure by 20% (1.20-fold) in healthy subjects, compared with administration of caffeine alone. At the clinically relevant dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (<2-fold increase in AUC).

Substances that are substrates of transporters

In vitro evaluations indicated that ribociclib has a potential to inhibit the activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit

a narrow therapeutic index, including but not limited to digoxin, pitavastatin, pravastatin, rosuvastatin and metformin.

Drug-food interactions

Kisqali can be administered with or without food (see sections 4.2 and 5.2).

Medicinal products that elevate gastric pH

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 study; however, altered ribociclib absorption was not observed in population pharmacokinetic and non-compartmental pharmacokinetic analyses.

Drug-drug interaction between ribociclib and letrozole

Data from a clinical study in patients with breast cancer and population pharmacokinetic analysis indicated no drug interaction between ribociclib and letrozole following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and anastrozole

Data from a clinical study in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and fulvestrant

Data from a clinical study in patients with breast cancer indicated no clinically relevant effects of fulvestrant on ribociclib exposure following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and tamoxifen

Data from a clinical study in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2-fold following co-administration of ribociclib and tamoxifen.

Drug-drug interactions between ribociclib and oral contraceptives

Drug-drug interaction studies between ribociclib and oral contraceptives have not been conducted (see section 4.6).

Anticipated interactions

Anti-arrhythmic medicinal products and other medicinal products that may prolong the QT interval

Co-administration of Kisqali with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol), and other medicinal products that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron) should be avoided (see section 4.4). Kisqali is also not recommended to be used in combination with tamoxifen (see sections 4.1, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

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

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.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman (see section 5.3). Kisqali is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breast-fed infant or the effects of ribociclib on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Patients receiving Kisqali should not breast-feed for at least 21 days after the last dose.

Fertility

There are no clinical data available regarding effects of ribociclib on fertility. Based on animal studies, ribociclib may impair fertility in males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety evaluation of Kisqali is based on the pooled dataset from 1,065 patients who received Kisqali in combination with endocrine therapy (N=582 in combination with an aromatase inhibitor and N=483 in combination with fulvestrant) and who were included in the randomised, double-blind, placebo-controlled phase III clinical studies (MONALEESA-2, MONALEESA-7 NSAI subgroup and MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer.

The median duration of exposure to Kisqali treatment across the pooled phase III studies dataset was 16.5 months, with 61.7% patients exposed ≥ 12 months.

Dose reduction due to adverse events, regardless of causality, occurred in 37.3% of patients receiving Kisqali in the phase III clinical studies regardless of the combination and permanent discontinuation was reported in 7.0% of patients receiving Kisqali and any combination in the phase III clinical studies.

The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency $\geq 20\%$ and $\geq 2\%$, respectively) in the pooled dataset for which the frequency for Kisqali plus any combination exceeds the frequency for placebo plus any combination were infections, neutropenia, leukopenia, headache, cough, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash, and infections, neutropenia, leukopenia, anaemia, abnormal liver function tests, lymphopenia, hypophosphataemia and vomiting respectively.

Tabulated list of adverse reactions

Adverse drug reactions from the phase III clinical studies (Table 6) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available data).

Table 6 Adverse drug reactions observed in the three phase III clinical studies

Adverse drug reaction	Frequency
Infections and infestations	
Infections ¹	Very common
Blood and lymphatic system disorders	
Neutropenia, leukopenia, anaemia	Very common
Lymphopenia, thrombocytopenia, febrile neutropenia	Common
Metabolism and nutrition disorders	
Decreased appetite	Very common
Hypocalcaemia, hypokalaemia, hypophosphataemia	Common
Nervous system disorders	
Headache, dizziness	Very common
Vertigo	Common
Eye disorders	
Lacrimation increased, dry eye	Common
Cardiac disorders	
Syncope	Common
Respiratory, thoracic and mediastinal disorders	
Dyspnoea, cough	Very common
Gastrointestinal disorders	
Nausea, diarrhoea, vomiting, constipation, stomatitis, abdominal pain ²	Very common
Dysgeusia, dyspepsia	Common
Hepatobiliary disorders	
Hepatotoxicity ³	Common
Skin and subcutaneous tissue disorders	
Alopecia, rash ⁴ , pruritus	Very common
Erythema, dry skin, vitiligo	Common
Musculoskeletal and connective tissue disorders	
Back pain	Very common
General disorders and administration site conditions	
Fatigue, peripheral oedema, asthenia, pyrexia	Very common
Dry mouth, oropharyngeal pain	Common
Investigations	
Abnormal liver function tests ⁵	Very common
Blood creatinine increased, electrocardiogram QT prolonged	Common
¹ Infections: urinary tract infections, respiratory tract infections, gastroenteritis, sepsis (<1%).	
² Abdominal pain: abdominal pain, abdominal pain upper.	
³ Hepatotoxicity: hepatocellular injury, drug-induced liver injury (<1%), hepatotoxicity, hepatic failure, autoimmune hepatitis (single case).	
⁴ Rash: rash, rash maculopapular, rash pruritic.	
⁵ Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.	

Description of selected adverse drug reactions

Neutropenia

Neutropenia was the most frequently reported adverse drug reaction (73.7%) and a grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 58.6% of patients receiving Kisqali plus any combination in the phase III studies.

Among the patients who had grade 2, 3 or 4 neutropenia, the median time to onset was 16 days, for those patients who had an event. The median time to resolution of grade ≥ 3 (to normalisation or grade < 3) was 12 days in the Kisqali plus any combination arms following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in about 1.4% of patients exposed to Kisqali in the phase III studies. Patients should be instructed to report any fever promptly.

Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Treatment discontinuation due to neutropenia was low (0.8%) (see sections 4.2 and 4.4).

Hepatobiliary toxicity

In the phase III clinical studies, hepatobiliary toxicity events occurred in a higher proportion of patients in the Kisqali plus any combination arms compared with the placebo plus any combination arms (23.2% versus 16.5%, respectively), with more grade 3/4 adverse events reported in the patients treated with Kisqali plus any combination (11.4% versus 5.4%, respectively). Increases in transaminases were observed. Grade 3 or 4 increases in ALT (9.7% versus 1.5%) and AST (6.7% versus 2.1%) were reported in the Kisqali and placebo arms, respectively. Concurrent elevations in ALT or AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301 [MONALEESA-2], whose levels recovered to normal within 154 days and 2 patients in Study F2301 [MONALEESA-3], whose levels recovered to normal in 121 and 532 days, respectively, after discontinuation of Kisqali). There were no such cases reported in Study E2301 (MONALEESA-7).

Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 10.4% of Kisqali plus any combination treated patients, primarily due to ALT increased (6.9%) and/or AST increased (6.1%). Discontinuation of treatment with Kisqali plus any combination due to abnormal liver function tests or hepatotoxicity occurred in 2.3% and 0.4% of patients respectively (see sections 4.2 and 4.4).

In the phase III clinical studies, 83.2% (89/107) of grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment. Among the patients who had grade 3 or 4 ALT/AST elevation, the median time to onset was 85 days for the Kisqali plus any combination arms. The median time to resolution (to normalisation or grade ≤ 2) was 22 days in the Kisqali plus any combination arms.

QT prolongation

In study E2301 (MONALEESA-7), the observed mean QTcF increase from baseline was approximately 10 msec higher in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup, suggesting that tamoxifen alone had a QTcF prolongation effect which can contribute to the QTcF values observed in the Kisqali plus tamoxifen group. In the placebo arm, a QTcF interval increase of > 60 msec from baseline occurred in 6/90 (6.7%) patients receiving tamoxifen and in no patients receiving a NSAI (see section 5.2). A QTcF interval increase of > 60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a NSAI. Kisqali is not recommended to be used in combination with tamoxifen (see section 5.1).

In the phase III clinical studies 8.4% of patients in the Kisqali plus aromatase inhibitor or fulvestrant arms and 3.2% in the placebo plus aromatase inhibitor or fulvestrant arms had at least one event of QT interval prolongation (including ECG QT prolonged and syncope). Review of ECG data showed 14 patients (1.3%) had > 500 msec post-baseline QTcF value, and 59 patients (5.6%) had a > 60 msec

increase from baseline in QTcF intervals. There were no reported cases of torsade de pointes. Dose interruptions/adjustments were reported in 2.3% of Kisqali plus aromatase inhibitor or fulvestrant treated patients due to electrocardiogram QT prolonged and syncope.

The analysis of ECG data showed 52 patients (4.9%) and 11 patients (1.4%) with at least one >480 msec post-baseline QTcF for the Kisqali plus aromatase inhibitor or fulvestrant arms and the placebo plus aromatase inhibitor or fulvestrant arms, respectively. Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was 15 days regardless of the combination and these changes were reversible with dose interruption and/or dose reduction (see sections 4.2, 4.4 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via [the national reporting system listed in Appendix V](#).

4.9 Overdose

There is only limited experience with reported cases of overdosage with Kisqali. In the event of an overdose, symptoms such as nausea and vomiting may occur. In addition, haematological (e.g. neutropenia, thrombocytopenia) toxicity and possible QTc prolongation may occur. General supportive care should be initiated in all cases of overdosage as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE42

Mechanism of action

Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6, resulting in 50% inhibition (IC_{50}) values of 0.01 (4.3 ng/ml) and 0.039 μ M (16.9 ng/ml) in biochemical assays, respectively. 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 led to tumour regressions which correlated with inhibition of pRb phosphorylation.

In vivo studies using patient-derived oestrogen receptor-positive breast cancer xenograft model combinations of ribociclib and antioestrogens (i.e. letrozole) resulted in superior tumour growth inhibition with sustained tumour regression and delayed tumour regrowth after stopping dosing compared to each substance alone. Additionally, *in vivo* antitumour activity of ribociclib in combination with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts and the combination with fulvestrant resulted in complete tumour growth inhibition.

When tested in a panel of breast cancer cell lines with known ER status, ribociclib demonstrated to be more efficacious in ER+ breast cancer cell lines than in the ER- ones. In the preclinical models tested so far, intact pRb was required for ribociclib activity.

Cardiac electrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated QTcF mean change from baseline for 600 mg Kisqali in combination with NSAID or fulvestrant was 22.0 msec (90% CI: 20.56, 23.44) and 23.7 msec (90% CI: 22.31, 25.08), respectively at the geometric mean C_{max} at steady-state compared to 34.7 msec (90% CI: 31.64, 37.78) in combination with tamoxifen (see section 4.4).

Clinical efficacy and safety

Study CLEE011A2301 (MONALEESA-2)

Kisqali was evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone.

A total of 668 patients were randomised in a 1:1 ratio to receive either Kisqali 600 mg and letrozole (n=334) or placebo and letrozole (n=334), stratified according to the presence of liver and/or lung metastases (Yes [n=292 (44%)] versus No [n=376 (56%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg once daily for 28 days. Patients were not allowed to cross over from placebo to Kisqali during the study or after progression of disease.

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% patients were older than 65 years, including 69 patients older than 75 years. The patients included were Caucasian (82.2%), Asian (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. In the Kisqali arm 43.7% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 52.4% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to study entry. 34.1% of patients were *de novo*. 20.7% of patients had bone-only disease and 59.0% of patients had visceral disease. Patients with prior (neo)adjuvant therapy with anastrozole or letrozole must have completed this therapy at least 12 months before study randomisation.

The primary endpoint for the study was met at the planned interim analysis conducted after observing 80% of targeted progression-free survival (PFS) events using Response Evaluation Criteria in Solid Tumours (RECIST v1.1), based on the investigator assessment in the full population (all randomised patients), and confirmed by a blinded independent central radiological assessment.

The efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (hazard ratio of 0.556, 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329) with clinically meaningful treatment effect.

The global health status/QoL data showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole arm.

A more mature update of efficacy data (02 January 2017 cut-off) is provided in Tables 7 and 8.

Median PFS was 25.3 months (95% CI: 23.0, 30.3) for ribociclib plus letrozole treated patients and 16.0 months (95% CI: 13.4, 18.2) for patients receiving placebo plus letrozole. 54.7% of patients receiving ribociclib plus letrozole were estimated to be progression-free at 24 months compared with 35.9% in the placebo plus letrozole arm.

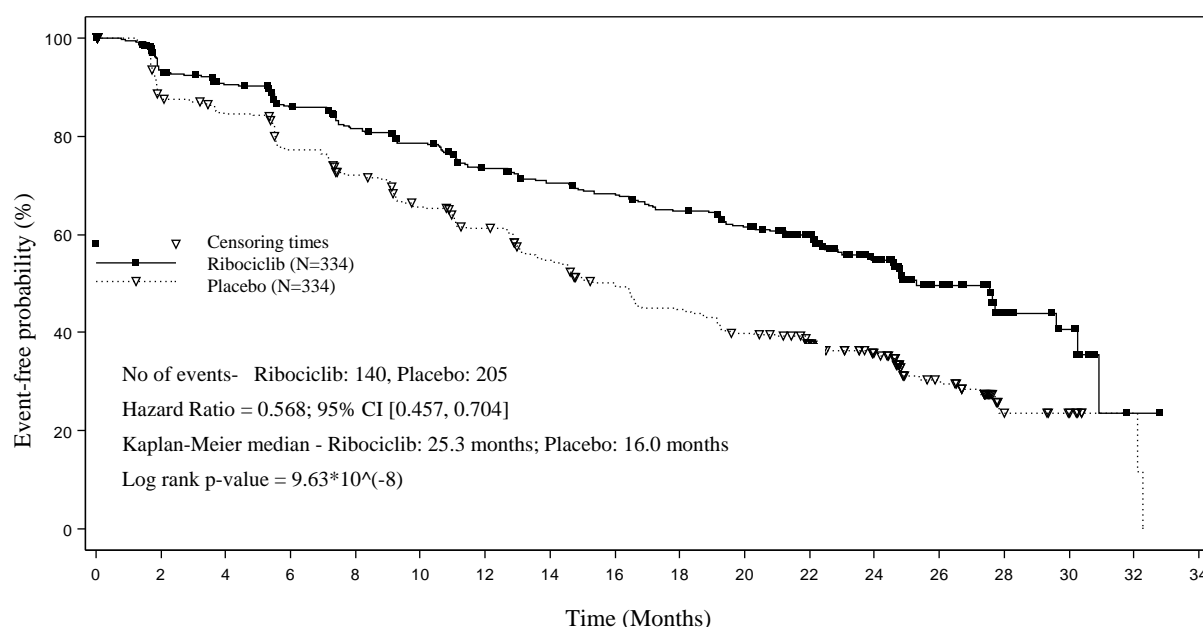
There was no statistically significant difference in overall survival (OS) between the Kisqali plus letrozole arm and the placebo plus letrozole arm (HR 0.746 [95% CI: 0.517, 1.078]). OS data remain

immature.

Table 7 MONALEESA-2 - Efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cut-off)

	Updated analysis (02 January 2017 cut-off)	
	Kisqali plus letrozole N=334	Placebo plus letrozole N=334
Progression-free survival		
Median PFS [months] (95% CI)	25.3 (23.0-30.3)	16.0 (13.4-18.2)
Hazard ratio (95% CI)	0.568 (0.457-0.704)	
p-value ^a	9.63×10 ⁻⁸	
CI=confidence interval; N=number of patients;		
^a p-value is obtained from the one-sided stratified log-rank test.		

Figure 1 MONALEESA-2 - Kaplan-Meier plot of PFS based on investigator assessment (02 January 2017 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

A series of pre-specified subgroup PFS analyses was performed based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in favour of the Kisqali plus letrozole arm was observed in all individual patient subgroups of age, race, prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease. This was evident for patients with liver and/or lung metastases (HR of 0.561 [95% CI: 0.424, 0.743], median progression-free survival [mPFS] 24.8 months for Kisqali plus letrozole versus 13.4 months for letrozole alone), or without liver and/or lung metastases (HR of 0.597 [95% CI: 0.426, 0.837], mPFS 27.6 months versus 18.2 months).

Updated results for overall response and clinical benefit rates are displayed in Table 8.

Table 8 MONALEESA-2 - Efficacy results (ORR, CBR) based on investigator assessment(02 January 2017 cut-off)

Analysis	Kisqali + letrozole (%, 95% CI)	Placebo + letrozole (%, 95% CI)	p-value ^c
Full analysis set	N=334	N=334	
Overall response rate^a	42.5 (37.2, 47.8)	28.7 (23.9, 33.6)	9.18×10^{-5}
Clinical benefit rate^b	79.9 (75.6, 84.2)	73.1 (68.3, 77.8)	0.018
Patients with measurable disease	N=257	N=245	
Overall response rate^a	54.5 (48.4, 60.6)	38.8 (32.7, 44.9)	2.54×10^{-4}
Clinical benefit rate^b	80.2 (75.3, 85.0)	71.8 (66.2, 77.5)	0.018
^a ORR: Overall response rate = proportion of patients with complete response + partial response ^b CBR: Clinical benefit rate = proportion of patients with complete response + partial response (+ stable disease or non-complete response/Non-progressive disease ≥ 24 weeks) ^c p-values are obtained from one-sided Cochran-Mantel-Haenszel chi-square test			

Study CLEE011E2301 (MONALEESA-7)

Kisqali was evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of pre- and perimenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer in combination with a NSAI or tamoxifen plus goserelin versus placebo in combination with a NSAI or tamoxifen plus goserelin. Patients in MONALEESA-7 had not received prior endocrine treatment in the advanced breast cancer setting.

A total of 672 patients were randomised in a 1:1 ratio to receive either Kisqali 600 mg plus NSAI/tamoxifen plus goserelin (n=335) or placebo plus NSAI/tamoxifen plus goserelin (n=337), stratified according to: the presence of liver and/or lung metastases (Yes [n=344 (51.2%)] versus No [n=328 (48.8%)]), prior chemotherapy for advanced disease (Yes [n=120 (17.9%)] versus No [n=552 (82.1%)]), and endocrine combination partner (NSAI and goserelin [n=493 (73.4%)] versus tamoxifen and goserelin [n=179 (26.6%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen (20 mg) orally once daily for 28 days, and goserelin (3.6 mg) subcutaneously every 28 days, until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression. Switching the endocrine combination partners was also not permitted.

Patients enrolled in this study had a median age of 44 years (range 25 to 58) and 27.7% of patients were younger than 40 years old. The majority of patients included were Caucasian (57.7%), Asian (29.5%) or Black (2.8%) and nearly all patients (99.0%) had a baseline ECOG performance status of 0 or 1. Prior to study entry, of these 672 patients, 14% of patients had received prior chemotherapy for metastatic disease, 32.6% of patients had received chemotherapy in the adjuvant and 18.0% in the neoadjuvant setting; 39.6% had received endocrine therapy in the adjuvant setting and 0.7% in the neoadjuvant setting. In study E2301 40.2% of patients had *de novo* metastatic disease, 23.7% had bone-only disease, and 56.7% had visceral disease.

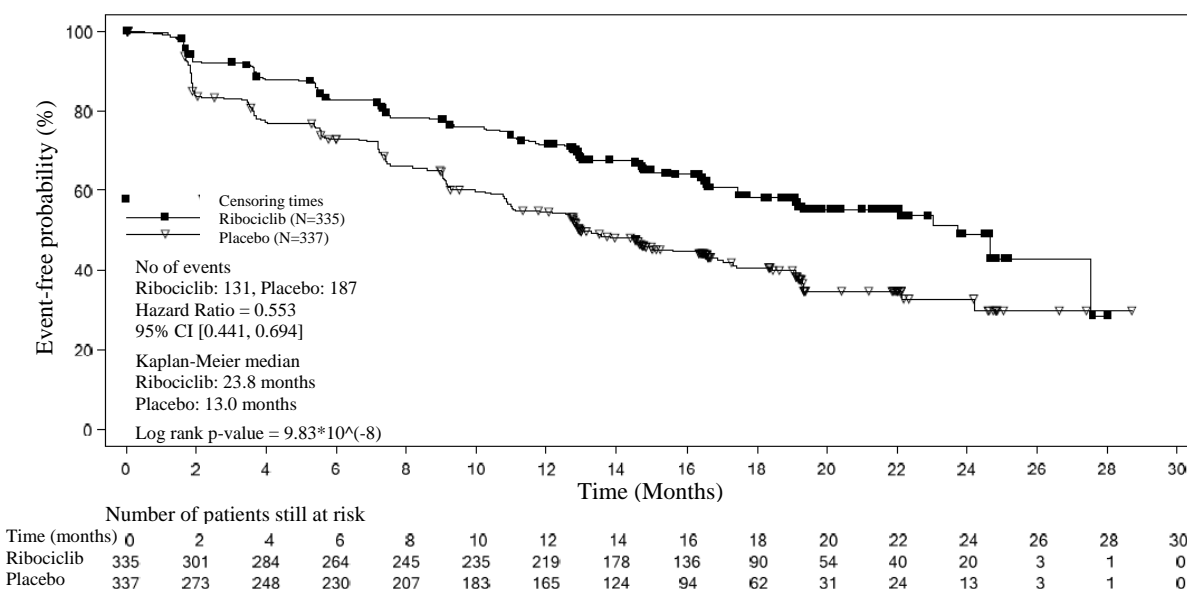
The study met the primary endpoint at the primary analysis conducted after 318 progression-free survival (PFS) events based on the investigator assessment using RECIST v1.1 criteria in the full analysis set (all randomised patients). The primary efficacy results were supported by PFS results based on blinded independent central radiological assessment. The median follow-up time at the time of primary PFS analysis was 19.2 months.

In the overall study population, the efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus NSAI/tamoxifen plus goserelin compared to patients receiving placebo plus NSAI/tamoxifen plus goserelin (hazard ratio of 0.553, 95% CI: 0.441, 0.694, one-sided stratified log-rank test p-value 9.83×10^{-8}) with clinically meaningful treatment effect.

Median PFS was 23.8 months (95% CI: 19.2, NE) for Kisqali plus NSAI/tamoxifen plus goserelin treated patients and 13.0 months (95% CI: 11.0, 16.4) for patients receiving placebo plus NSAI/tamoxifen plus goserelin.

Distribution of PFS is summarised in the Kaplan-Meier curve for PFS in Figure 2.

Figure 2 MONALEESA-7 - Kaplan-Meier plot of PFS in overall population based on investigator assessment



The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomised patients were supportive of the primary efficacy results based on the investigator's assessment (hazard ratio of 0.427; 95% CI: 0.288, 0.633).

At the time of the primary PFS analysis overall survival data were not mature with 89 (13%) of deaths (HR 0.916 [95% CI: 0.601, 1.396]).

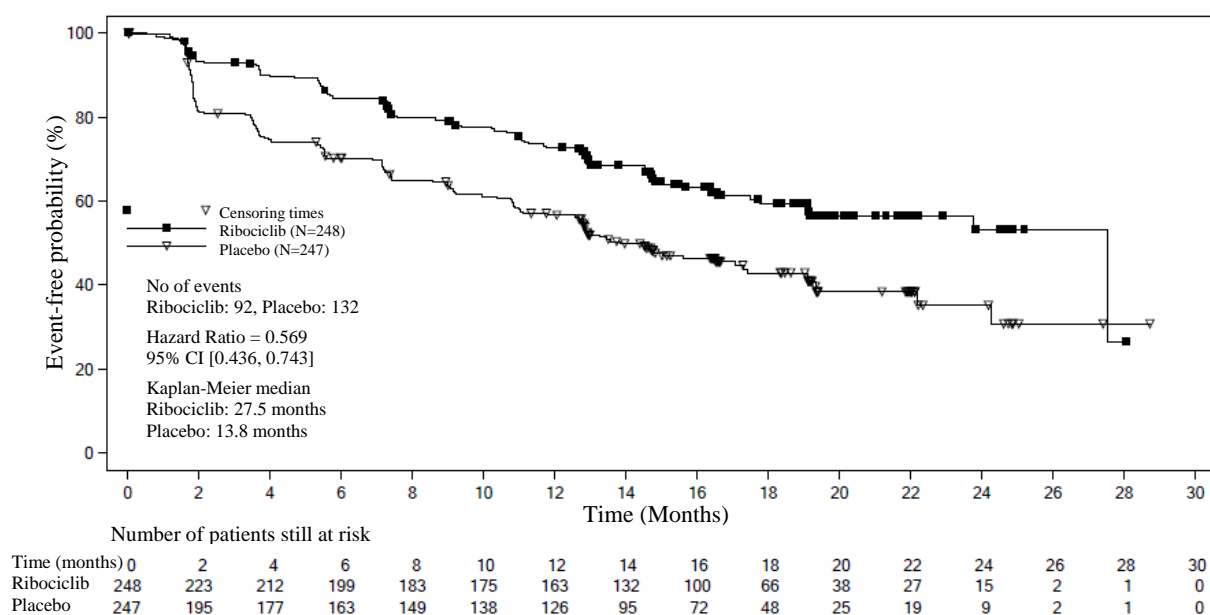
Overall response rate (ORR) per investigator assessment based on RECIST v1.1 was higher in the Kisqali arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6, p=0.00098). The observed clinical benefit rate (CBR) was higher in Kisqali arm (79.1%; 95% CI: 74.8:83.5) compared to placebo arm (69.7%; 95% CI: 64.8:74.6, p=0.002).

In the pre-specified subgroup analysis of 495 patients who had received Kisqali or placebo in combination with NSAI plus goserelin, the median PFS was 27.5 months (95% CI: 19.1, NE) in the Kisqali plus NSAI subgroup and 13.8 months (95% CI: 12.6, 17.4) in the placebo plus NSAI subgroup [HR: 0.569; 95% CI: 0.436, 0.743]. Efficacy results are summarised in Table 9 and the Kaplan-Meier curves for PFS are provided in Figure 3.

Table 9 MONALEESA-7 - Efficacy results (PFS) in patients who received NSAI

	Kisqali plus NSAI plus goserelin N=248	Placebo plus NSAI plus goserelin N=247
Progression free survival^a		
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)	
CI=confidence interval; N=number of patients; NE = Not estimable.		
^a – PFS based on investigator radiological assessment		

Figure 3 MONALEESA-7 – Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI



Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 10.

Table 10 MONALEESA-7 - Efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI

Analysis	Kisqali plus NSAI plus goserelin (%, 95% CI)	Placebo plus NSAI plus goserelin (%, 95% CI)
Full analysis set	N=248	N=247
Overall response rate (ORR)^a	39.1 (33.0, 45.2)	29.1 (23.5, 34.8)
Clinical benefit rate (CBR)^b	80.2 (75.3, 85.2)	67.2 (61.4, 73.1)
Patients with measurable disease	N=192	N=199
Overall response rate^a	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)
Clinical benefit rate^b	81.8 (76.3, 87.2)	63.8 (57.1, 70.5)

^aORR: proportion of patients with complete response + partial response
^bCBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease ≥24 weeks)

Results in the Kisqali plus NSAI subgroup were consistent across subgroups of age, race, prior adjuvant/ neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.

Study CLEE011F2301 (MONALEESA-3)

Kisqali was evaluated in a randomised double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of men and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who had received no or only one line of prior endocrine treatment, in combination with fulvestrant versus fulvestrant alone.

A total of 726 female patients were randomised in a 2:1 ratio to receive either Kisqali 600 mg and fulvestrant (n=484) or placebo and fulvestrant (n=242), stratified according to the presence of liver and/or lung metastases (Yes [n= 351 (48.3%)] versus No [n=375 (51.7%)] and according to prior endocrine therapy (A [n=354 (48.8%)] versus B [n=372 (51.2%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali 600 mg or placebo were

given orally daily for 21 consecutive days followed by 7 days off treatment in combination with fulvestrant 500 mg intramuscularly once daily on Days 1 and 15 in Cycle 1 and Day 1 of each subsequent 28-day cycle. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression.

Patients enrolled in this study had a median age of 63 years (range 31 to 89). 46.7% of patients were of age 65 years and older, including 13.8% patients of age 75 years and older. The patients included were Caucasian (85.3%), Asian (8.7%) or Black (0.7%) 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 whom 19.1% had *de novo* metastatic disease). Prior to study entry 42.7% of patients had received chemotherapy in the adjuvant and 13.1% in the neoadjuvant setting, while 58.5% had received endocrine therapy in the adjuvant and 1.4% in the neoadjuvant setting and 21% had received prior endocrine therapy in the advanced breast cancer setting. In study F2301 21.2% had bone-only disease and 60.5% had visceral disease.

The study met the primary endpoint at the primary analysis conducted after 361 progression-free survival (PFS) events based on the investigator assessment and using RECIST v1.1 criteria in the full analysis set (all randomised patients). The primary efficacy results were supported by PFS results based on blinded independent central radiological assessment. The median follow-up time at the time of primary PFS analysis was 20.4 months.

The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus fulvestrant compared to patients receiving placebo plus fulvestrant in the full analysis set (hazard ratio of 0.593, 95% CI: 0.480, 0.732, one-sided stratified log-rank test p-value 4.1×10^{-7}), with an estimated 41% reduction in relative risk of progression or death in favour of the Kisqali plus fulvestrant arm.

Median PFS was 20.5 months (95% CI: 18.5, 23.5) for Kisqali plus fulvestrant treated patients and 12.8 months (95% CI: 10.9, 16.3) for patients receiving placebo plus fulvestrant.

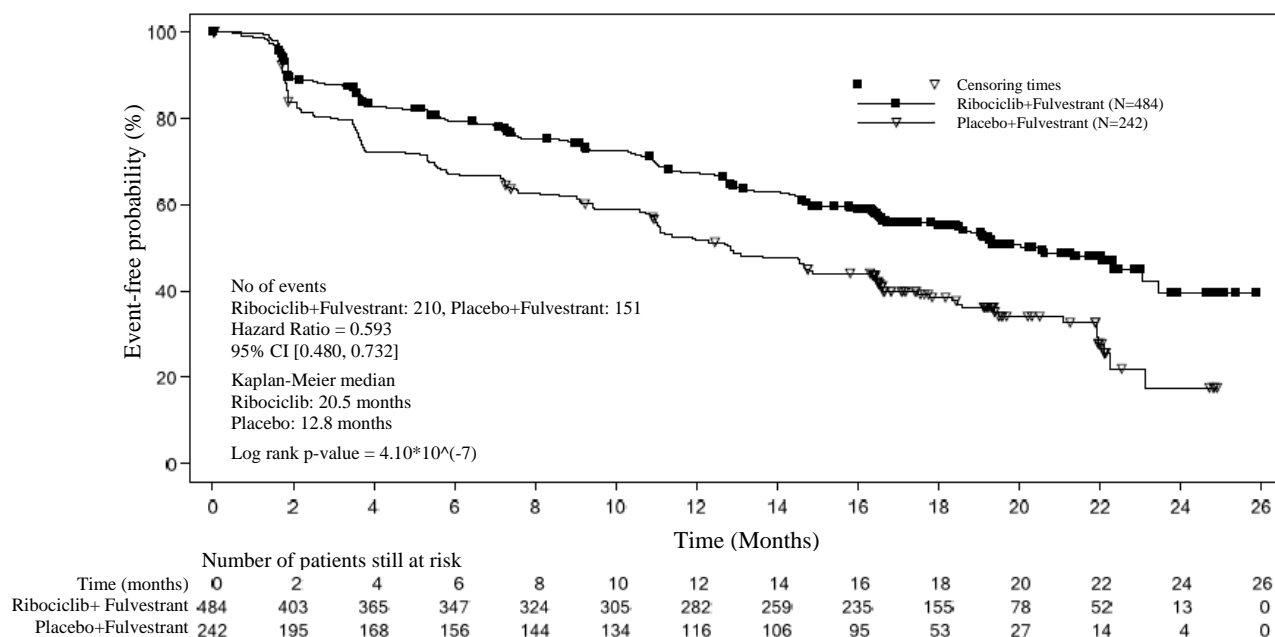
Distribution of PFS is summarised in Table 11 and in the Kaplan-Meier curve for PFS in Figure 4.

Table 11 MONALEESA-3 - Efficacy results (PFS) based on investigator radiological assessment

	Kisqali plus fulvestrant N=484	Placebo plus fulvestrant N=242
Progression free survival		
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 to 0.732)	
p-value ^a	0.0000410	

CI=confidence interval; N=number of patients; NE = Not estimable.
^a p-value is obtained from the one-sided stratified log-rank test.

Figure 4 MONALEESA-3 – Kaplan-Meier plot of PFS based on investigator assessment



The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomised patients were supportive of the primary efficacy results based on the investigator’s assessment (hazard ratio of 0.492; 95% CI: 0.345, 0.703).

At the time of the primary PFS analysis, overall survival data were not mature with 120 (16.5%) deaths (HR 0.670; [95% CI: 0.465, 0.964]).

Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 12.

Table 12 MONALEESA-3 - Efficacy results (ORR, CBR) based on investigator assessment

Analysis	Kisqali plus fulvestrant (%, 95% CI)	Placebo plus fulvestrant (%, 95% CI)
Full analysis set	N=484	N=242
Overall response rate (ORR)^a	32.4 (28.3, 36.6)	21.5 (16.3, 26.7)
Clinical benefit rate (CBR)^b	70.2 (66.2, 74.3)	62.8 (56.7, 68.9)
Patients with measurable disease	N=379	N=181
Overall response rate^a	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)
Clinical benefit rate^b	69.4 (64.8, 74.0).	59.7 (52.5, 66.8)

^aORR: proportion of patients with complete response + partial response
^bCBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease ≥24 weeks)

In the subgroup of patients who were treatment-naïve in the metastatic/advanced disease setting, the hazard ratio was of 0.577 (95% CI: 0.415, 0.802), with a median PFS not reached in the Kisqali arm and 18.3 months (95% CI: 14.8, 23.1) in the placebo arm.

In the subgroup of patients who had received up to one line of treatment for metastatic/advanced disease, the hazard ratio was of 0.565 (95% CI: 0.428, 0.744), with a median PFS of 14.6 months (95% CI: 12.5, 18.5) and 9.1 months (95% CI: 6.1, 11.1) in the Kisqali and placebo arms, respectively. Within this subgroup, the hazard ratio for the second line patients who had received prior endocrine therapy in the advanced breast cancer setting was 0.539 (95% CI: 0.333, 0.873), with a median PFS of 18.8 months (95% CI: 12.5, NE) and 11.4 months (95% CI: 3.7, 16.3) in the Kisqali and placebo arms,

respectively.

Hazard ratios based on pre-specified subgroup analysis of the patients treated with Kisqali plus fulvestrant showed consistent benefit across different subgroups including age, prior treatment (early or advanced), prior adjuvant/neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.

Elderly patients

Of all patients who received Kisqali in studies MONALEESA-2 and MONALEESA-3, representative proportions of patients were ≥ 65 years and ≥ 75 years of age (see section 5.1). No overall differences in safety or effectiveness of Kisqali were observed between these patients and younger patients (see section 4.2).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Kisqali in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50 mg to 1200 mg. Healthy subjects received single oral doses ranging from 400 mg to 600 mg or repeated daily doses (8 days) at 400 mg.

Absorption

The absolute bioavailability of ribociclib is not known.

The time to reach C_{\max} (T_{\max}) following ribociclib oral administration was between 1 and 4 hours. Ribociclib exhibited slightly over-proportional increases in exposure (C_{\max} and AUC) across the dose range tested (50 to 1200 mg). 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).

Food effect

Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib film-coated tablets with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib.

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and was independent of concentration (10 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 apparent volume of distribution at steady state (V_{ss}/F) was 1090 L based on population pharmacokinetic analysis.

Biotransformation

In vitro and *in vivo* studies indicated ribociclib is eliminated primarily via 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. The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide). Clinical activity (pharmacological and safety) of ribociclib was due primarily

to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolised, with unchanged drug accounting for 17.3% and 12.1% of the dose in faeces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in faeces and urine, respectively. Numerous other metabolites were detected in both faeces and urine in minor amounts ($\leq 2.78\%$ 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 and its metabolites are eliminated mainly via faeces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 91.7% of the total administered radioactive dose was recovered within 22 days; faeces was the major route of excretion (69.1%), with 22.6% of the dose recovered in urine.

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. This analysis is limited by the small sample sizes for most of the dose cohorts with a majority of the data coming from the 600 mg dose cohort.

Special populations

Renal impairment

Based on a population pharmacokinetic analysis that included 77 patients with normal renal function (eGFR ≥ 90 ml/min/1.73 m²), 76 patients with mild renal impairment (eGFR 60 to < 90 ml/min/1.73 m²) and 35 patients with moderate renal impairment (eGFR 30 to < 60 ml/min/1.73 m²), mild and moderate renal impairment had no effect on the exposure of ribociclib (see section 4.2). The pharmacokinetics of ribociclib in patients with severe renal impairment have not been studied.

Hepatic impairment

Based on a pharmacokinetic study in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section 4.2). The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.50 for C_{\max} ; 1.32 for AUC_{inf}) and severe (GMR: 1.34 for C_{\max} ; 1.29 for AUC_{inf}) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 breast cancer 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).

Effect of age, weight, gender and race

Population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight or gender on the systemic exposure of ribociclib that would require a dose adjustment. Data on differences in pharmacokinetics due to race are too limited to draw conclusions.

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 CYP2C9, CYP2C19 and CYP3A4 via PXR. Therefore, Kisqali is unlikely to affect substrates of these enzymes. *In vitro* data are not sufficient to exclude a potential of ribociclib to induce CYP2B6 via CAR.

Effect of transporters on ribociclib

Ribociclib is a substrate for P-gp *in vitro*, but based on mass balance data inhibition of P-gp or BCRP is unlikely to affect ribociclib exposure at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1, OATP1B3 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 P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. Ribociclib did not inhibit OAT1, OAT3 or MRP2 at clinically relevant concentrations *in vitro*.

5.3 Preclinical safety data

Safety pharmacology

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. There is also potential to induce incidences of premature ventricular contractions (PVCs) at elevated exposures (approximately 5-fold the anticipated clinical C_{max}).

Repeated-dose toxicity

Repeated-dose toxicity studies (treatment schedule of 3 weeks on/1 week off) of up to 27 weeks' duration in rats and up to 39 weeks' duration in dogs, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat-dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment-free period. Exposure to ribociclib in animals in the 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/Fertility

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the 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 any dose up to 300 mg/kg/day (which is likely at an exposure lower than or equal to patients' clinical exposure 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. The exposure to ribociclib was higher in milk than in plasma.

Genotoxicity

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a genotoxic potential of ribociclib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Crospovidone type A
Low-substituted hydroxypropylcellulose
Magnesium stearate
Colloidal anhydrous silica

Film coating

Iron oxide black (E172)
Iron oxide red (E172)
Soya lecithin (E322)
Polyvinyl alcohol (partially hydrolysed)
Talc
Titanium dioxide (E171)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE (polyvinylchloride/polychlorotrifluoroethylene) or PA/alu/PVC (polyamide/aluminium/polyvinylchloride) blisters containing 14 or 21 film-coated tablets.

Unit packs containing 21, 42 or 63 film-coated tablets and multipacks containing 63 (3 packs of 21), 126 (3 packs of 42) or 189 (3 packs of 63) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1221/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 August 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets
ribociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

21 film-coated tablets
42 film-coated tablets
63 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

Enter weekdays starting with the 1st day of treatment. Mark off circle for every tablet you take.

Take your dose once a day for 3 weeks followed by a 1-week break.

No Kisqali this week.

Day

Week

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1221/001	21 film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/002	21 film-coated tablets (in PA/alu/PVC blisters)
EU/1/17/1221/003	42 film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/004	42 film-coated tablets (in PA/alu/PVC blisters)
EU/1/17/1221/005	63 film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/006	63 film-coated tablets (in PA/alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kisqali 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets
ribociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 63 (3 packs of 21) film-coated tablets

Multipack: 126 (3 packs of 42) film-coated tablets

Multipack: 189 (3 packs of 63) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1221/007	63 (3 x 21) film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/008	63 (3 x 21) film-coated tablets (in PA/alu/PVC blisters)
EU/1/17/1221/009	126 (3 x 42) film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/010	126 (3 x 42) film-coated tablets (in PA/alu/PVC blisters)
EU/1/17/1221/011	189 (3 x 63) film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/012	189 (3 x 63) film-coated tablets (in PA/alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kisqali 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets
ribociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

21 film-coated tablets. Component of a multipack. Not to be sold separately.
42 film-coated tablets. Component of a multipack. Not to be sold separately.
63 film-coated tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

Enter weekdays starting with the 1st day of treatment. Mark off circle for every tablet you take.

Take your dose once a day for 3 weeks followed by a 1-week break.

No Kisqali this week.

Day

Week

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1221/007	63 (3 x 21) film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/008	63 (3 x 21) film-coated tablets (in PA/alu/PVC blisters)
EU/1/17/1221/009	126 (3 x 42) film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/010	126 (3 x 42) film-coated tablets (in PA/alu/PVC blisters)
EU/1/17/1221/011	189 (3 x 63) film-coated tablets (in PCTFE/PVC blisters)
EU/1/17/1221/012	189 (3 x 63) film-coated tablets (in PA/alu/PVC blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Kisqali 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Kisqali 200 mg film-coated tablets
ribociclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kisqali 200 mg film-coated tablets ribociclib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kisqali is and what it is used for
2. What you need to know before you take Kisqali
3. How to take Kisqali
4. Possible side effects
5. How to store Kisqali
6. Contents of the pack and other information

1. What Kisqali is and what it is used for

What Kisqali is

Kisqali contains the active substance ribociclib, which belongs to a group of medicines called cyclin-dependent kinase (CDK) inhibitors.

What Kisqali is used for

Kisqali is used in women with a type of breast cancer called hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer that is locally advanced or has spread to other parts of the body (metastatic). It is used in combination with an aromatase inhibitor or fulvestrant, which are used as hormonal anticancer therapies.

Women who have not reached menopause will also be treated with a medicine called a luteinising hormone releasing hormone (LHRH) agonist.

How Kisqali works

Kisqali works by blocking proteins called cyclin-dependent kinases 4 and 6, which are important for the growth and division of cells. Blocking these proteins can slow down the growth of cancer cells and delay the progression of your cancer.

If you have any questions about how Kisqali works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Kisqali

Follow all of your doctor's instructions carefully. They may differ from the general information in this leaflet.

Do not take Kisqali:

- if you are allergic to ribociclib, peanut, soya or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic, ask your doctor for advice.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Kisqali.

If any of the following apply to you, tell your doctor or pharmacist before taking Kisqali:

- If you have a fever, sore throat or mouth ulcers due to infections (signs of a low level of white blood cells).
- If you have any problems with your liver or have previously had any type of liver disease.
- If you have or have had heart disorders or heart rhythm disorders, such as an irregular heartbeat, including a condition called prolonged QT syndrome (QT interval prolongation) or low levels of potassium, magnesium, calcium or phosphorus in your blood.

Monitoring during your treatment with Kisqali

You will have regular blood tests before and during treatment with Kisqali to check your liver function and the amount of blood cells (white blood cells, red blood cells and platelets) and electrolytes (blood salts including potassium, calcium, magnesium and phosphate) in your body. Your heart activity will also be monitored before and during treatment with Kisqali with a test called an electrocardiogram (ECG). If necessary, your doctor may reduce your dose of Kisqali or temporarily stop it to allow your liver, blood cells, electrolyte levels or heart activity to recover. Your doctor may also decide to stop treatment with Kisqali permanently.

Children and adolescents

Kisqali is not to be used in children and adolescents under 18 years of age.

Other medicines and Kisqali

Before you take Kisqali, tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines or supplements obtained without a prescription, because these may influence the effect of Kisqali. This includes in particular:

- Tamoxifen, another medicine for the treatment of breast cancer.
- Some medicines used to treat fungal infections, such as ketoconazole, itraconazole, voriconazole or posaconazole.
- Some medicines used to treat HIV/AIDS such as ritonavir, saquinavir, indinavir, lopinavir, nelfinavir, telaprevir and efavirenz.
- Some medicines used to treat seizures or fits (anti-epileptics) such as carbamazepine and phenytoin.
- St. John's Wort (also known as *Hypericum perforatum*) - a herbal product used to treat depression and other conditions.
- Some medicines used to treat heart rhythm problems or high blood pressure such as amiodarone, disopyramide, procainamide, quinidine, sotalol and verapamil.
- Antimalarials such as chloroquine.
- Antibiotics such as clarithromycin, telithromycin, moxifloxacin, rifampicin, ciprofloxacin, levofloxacin and azithromycin.
- Some medicines used for sedation or anaesthesia such as midazolam.
- Some medicines used as antipsychotics such as haloperidol.
- Medicines used to treat angina such as bepridil.
- Methadone, used to treat pain or addiction to opioids.
- Medicines like intravenous ondansetron, used to prevent nausea and vomiting caused by chemotherapy (treatment with cancer medicines).

Kisqali may increase or decrease your blood levels of some other medicines. This includes in particular:

- Medicines used to treat symptoms of benign prostatic hyperplasia such as alfuzosin.

- Tamoxifen, another medicine used for the treatment of breast cancer.
- Antiarrhythmics such as amiodarone or quinidine.
- Antipsychotics such as pimozide or quetiapine.
- Medicines used to improve blood fat levels such as simvastatin or lovastatin, pitavastatin, pravastatin or rosuvastatin.
- Medicines used to treat high blood sugar levels (e.g. diabetes) such as metformin.
- Medicines used to treat cardiac disorders such as digoxin
- Medicines used to treat pulmonary arterial hypertension and erectile dysfunction such as sildenafil.
- Medicines used to treat low blood pressure or migraine such as ergotamine or dihydroergotamine.
- Some medicines used to treat epileptic fits or which are used for sedation or anaesthesia such as midazolam.
- Medicines used to treat sleep disorders such as triazolam.
- Analgesics such as alfentanil and fentanyl.
- Medicines used for the treatment of gastrointestinal disorders such as cisapride.
- Medicines used to prevent the rejection of an organ transplant such as tacrolimus, sirolimus and ciclosporin (also used to treat inflammation in rheumatoid arthritis and psoriasis).
- Everolimus, used for several types of cancer and tuberous sclerosis (also used to prevent the rejection of an organ transplant).

Make sure you tell your doctor of all medicines and supplements, including herbal medicines, that you are taking before you start treatment with Kisqali and if you are prescribed a new medicine after you have started treatment with Kisqali.

Ask your doctor or pharmacist if you are not sure if your medicine is one of the medicines listed above.

Kisqali with food and drink

You should not eat grapefruits or drink grapefruit juice during your treatment with Kisqali. It may change how Kisqali is processed in your body and may increase the amount of Kisqali in your bloodstream.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Your doctor will discuss with you the potential risks of taking Kisqali during pregnancy.

Pregnancy and women of childbearing potential

Kisqali should not be used during pregnancy since it may harm your unborn baby. If you are a woman of childbearing potential you should have a negative pregnancy test before starting treatment with Kisqali. You should use effective contraception (e.g. double-barrier contraception such as condom and diaphragm) while taking Kisqali and for at least 21 days after the last dose. Ask your doctor about options for effective contraception.

Breast-feeding

You should not breast-feed while taking Kisqali and for at least 21 days after the last dose.

Driving and using machines

Treatment with Kisqali may lead to tiredness, dizziness or spinning sensation. You should therefore be cautious when driving or using machines during your treatment with Kisqali.

Kisqali contains soya lecithin

If you are allergic to peanut or soya, do not use this medicine.

3. How to take Kisqali

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Your doctor, pharmacist or nurse will tell you exactly how many tablets to take and which days to take them on. Check with your doctor, pharmacist or nurse if you are not sure. Do not change the Kisqali dose or schedule without talking to your doctor.

Do not exceed the recommended dose prescribed by your doctor.

How much Kisqali to take

- The recommended starting dose of Kisqali is 600 mg (3 tablets of 200 mg) once daily. Your doctor will tell you exactly how many tablets of Kisqali to take; in certain situations your doctor may instruct you to take a lower dose of Kisqali, e.g. 400 mg (2 tablets of 200 mg) once daily or 200 mg (1 tablet of 200 mg) once daily.
- A treatment cycle lasts 28 days. Take Kisqali once a day only on days 1 to 21 of a 28-day cycle. The outer carton of the Kisqali pack includes a “calendar tool” which allows you to track your daily Kisqali dose by marking off a circle for every tablet you take over the 28-day cycle. You should not take Kisqali on days 22 to 28 of the cycle.

It is very important to follow your doctor’s instructions. If you get certain side effects your doctor may ask you to take a lower dose, interrupt your treatment with Kisqali, or stop it permanently.

When to take Kisqali

Take Kisqali once daily at the same time each day, preferably in the morning. This will help you to remember to take your medicine.

How to take Kisqali

Kisqali tablets should be swallowed whole (tablets should not be chewed, crushed or split before swallowing). Do not take a tablet that is broken, cracked or otherwise damaged.

Kisqali with food and drink

You should take Kisqali once daily every day at the same time, preferably in the morning. You may take it with or without food.

How long to take Kisqali

Take Kisqali once a day on days 1 to 21 of a 28-day cycle. Continue Kisqali treatment for as long as your doctor tells you to.

This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you take more Kisqali than you should

If you take too many tablets, or if someone else takes your medicine, contact a doctor or hospital for advice immediately. Show the Kisqali packet. Medical treatment may be necessary.

If you miss a dose of Kisqali

If you vomit after taking the dose or forget a dose, skip the missed dose that day. Take the next dose at your usual time.

Do not take a double dose to make up for a missed dose. Instead, wait until it is time for your next dose and then take your usual dose.

If you stop taking Kisqali

Stopping your treatment with Kisqali may cause your condition to get worse. Do not stop taking Kisqali unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious

Tell your doctor immediately if you get any of the following symptoms during treatment with Kisqali:

- Fever, chills, weakness and frequent infections with symptoms such as sore throat or mouth ulcers (signs of a low level of different types of blood cells). *Very common (may affect more than 1 in 10 people).*
- Tiredness, itchy yellow skin or yellowing of the whites of your eyes, nausea or vomiting, loss of appetite, pain in the upper right side of the belly (abdomen), dark or brown urine, bleeding or bruising more easily than normal (these may be signs of a liver problem). *Common (may affect up to 1 in 10 people).*
- Chest pain or discomfort, changes in heart beat (fast or slow), palpitations, lightheadedness, fainting, dizziness, lips turning blue colour, shortness of breath, swelling (oedema) of your lower limbs or skin (these may be signs of heart problems). *Common (may affect up to 1 in 10 people).*
- Serious infection with increased heart rate, shortness of breath or rapid breathing, fever and chills (these may be signs of sepsis which is an infection in the blood system which may be life threatening). *Uncommon (may affect up to 1 in 100 people).*

Your doctor may ask you to take a lower dose, interrupt your treatment with Kisqali, or stop it permanently.

Other possible side effects

Other side effects include the following listed below. If these side effects become severe, tell your doctor, pharmacist or nurse.

Very common (may affect more than 1 in 10 people)

- Tiredness, pale skin (potential sign of a low level of red blood cells, anaemia)
- Sore throat, runny nose, fever (signs of a respiratory tract infection)
- Painful and frequent urination (signs of a urinary tract infection)
- Reduced appetite
- Shortness of breath, difficulty breathing
- Back pain
- Nausea (feeling sick)
- Diarrhoea
- Vomiting
- Constipation
- Mouth sores with gum inflammation (stomatitis)
- Abdominal (belly) pain
- Hair loss or hair thinning (alopecia)
- Rash
- Itching (pruritus)
- Tiredness (fatigue)
- Weakness (asthenia)
- Fever (pyrexia)
- Headache
- Swollen hands, ankles or feet (peripheral oedema)
- Dizziness or light headedness
- Cough

Common (may affect up to 1 in 10 people)

- Abdominal pain, nausea, vomiting and diarrhoea (signs of gastroenteritis, which is an infection of the gastrointestinal tract)
- Spontaneous bleeding or bruising (signs of a low level of blood platelets)
- Watering eyes
- Dry eyes
- Reduced level of calcium in the blood, which may sometimes lead to cramps
- Reduced level of phosphate in the blood
- Strange taste in the mouth (dysgeusia)
- Upset stomach, indigestion, heartburn (dyspepsia)
- Abnormal kidney blood test result (high level of creatinine in the blood)
- Skin reddening (erythema)
- Spinning sensation (vertigo)
- Dry skin
- Loss of skin colour in patches (vitiligo)
- Dry mouth
- Sore throat (oropharyngeal pain)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kisqali

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kisqali contains

- The active substance is ribociclib. Each film-coated tablet contains ribociclib succinate equivalent to 200 mg ribociclib.
- The other ingredients are:
Tablet core: microcrystalline cellulose; crospovidone type A; low-substituted hydroxypropylcellulose; magnesium stearate; colloidal anhydrous silica.
Coating material: iron oxide black (E172); iron oxide red (E172); soya lecithin (E322); polyvinyl alcohol (partially hydrolysed); talc; titanium dioxide (E171); xanthan gum.

What Kisqali looks like and contents of the pack

Kisqali is supplied as film-coated tablets in aluminum blisters.

The film-coated tablets are light greyish violet in colour, unscored, round, debossed with “RIC” on

one side and “NVR” on the other side.

The following pack sizes are available: Packs containing 21, 42 or 63 film-coated tablets and multipacks containing 63 (3 packs of 21), 126 (3 packs of 42) or 189 (3 packs of 63) film-coated tablets.

Kisqali packs containing 63 tablets are intended for use by patients taking the full ribociclib daily dose of 600 mg (3 tablets once daily).

Kisqali packs containing 42 tablets are intended for use by patients taking the reduced ribociclib daily dose of 400 mg (2 tablets once daily).

Kisqali packs containing 21 tablets are intended for use by patients taking the lowest ribociclib daily dose of 200 mg (1 tablet once daily).

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>