▼ 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 "Undesirable effects" for how to report adverse reactions.

NAME OF THE MEDICINAL PRODUCT. Kisqali 200 mg film-coated tablets. **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 full leaflet.**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.

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. **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 full leaflet). 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 events (AEs) 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, 4,5 and 6 summarise recommendations for dose interruption, reduction or discontinuation of Kisqali in the management of specific AEs. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see full leaflet).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.

* 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

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	1. The dose should be interrupted. 2. If QTcF prolongation resolves to <481 msec, resume treatment at the next lower dose level. 3. 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	If QTcF is greater than 500 msec, interrupt Kisqali until QTcF is <481 msec then resume Kisqali at next lower dose level. 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.

Table 5 Dose modification and management – ILD/pneumonitis

	Grade 1* (asymptomatic)	**Grade 2*** (symptomatic)	**Grade 3 or 4*** (severe)
ILD/pneumonitis	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 next lower dose level**.	Discontinue Kisqali

*Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)
**An individualised benefit-risk assessment should be performed when considering resuming Kisqali
ILD = interstitial lung disease

Table 6 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, QT interval prolongation and ILD/pneumonitis.
** 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 full leaflet).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 full leaflet).*Special populations. Renal impairment*. No dose adjustment is necessary in patients with mild or moderate renal impairment. A starting dose of 200 mg is recommended in patients with severe renal impairment. Kisqali has not been studied in breast cancer patients with severe renal impairment (see full leaflet). *Hepatic impairment.* 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 (see full leaflet). *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 full leaflet). 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. **CONTRA-INDICATIONS**. Hypersensitivity to the active substance or to peanut, soya or any of the excipients listed in the full leaflet.**UNDESIRABLE EFFECTS.**
Summary of the safety profile. The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥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.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. Tabulated list of adverse reactions. 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. Additional ADRs were identified post-marketing. The median duration of exposure to Kisqali treatment across the pooled phase III studies dataset was 21.7 months, with 61.7% patients exposed ≥12 months. Adverse drug reactions from the phase III clinical studies (Table 7) 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 7 Adverse drug reactions observed in the three phase III clinical studies and during postmarketing experience

Adverse drug reaction	**Frequency**
Infections and infestations	
Infections[1]	Very common
Blood and lymphatic system disorders	
Neutropenia, leukopenia, anaemia, lymphopenia Thrombocytopenia, febrile neutropenia	Very common Common
Metabolism and nutrition disorders	
Decreased appetite Hypocalcaemia, hypokalaemia, hypophosphataemia	Very common Common
Nervous system disorders	
Headache, dizziness Vertigo	Very common 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], dyspepsia	Very common
Dysgeusia	Common
Hepatobiliary disorders	
Hepatotoxicity[3]	Common
Skin and subcutaneous tissue disorders	
Alopecia, rash[4], pruritus	Very common
Erythema, dry skin, vitiligo	Common
Toxic epidermal necrolysis (TEN)*	Not known
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.
* Adverse reactions reported during post-marketing experience. These are derived from spontaneous reports for which it is not always possible to reliably establish frequency or a causal relationship to exposure to the medicinal product.

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%).*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.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. 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.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. *Patients with renal impairment.* In the three pivotal studies, 341 patients with mild renal impairment and 97 patients with moderate renal impairment were treated with ribociclib. No patient with severe renal impairment was enrolled (see full leaflet). There was a correlation between the degree of renal impairment at baseline and blood creatinine values during the treatment. Slightly increased rates of QT prolongation and thrombocytopenia were observed in patients with mild or moderate renal impairment. For monitoring and dose adjustment recommendations for these toxicities see full leaflet.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. **MARKETING AUTHORISATION HOLDER.** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER(S)**. EU/1/17/1221/001-012. **MODE OF DELIVERY.** Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT**. 28 May 2021. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.