United Kingdom Prescribing Information:

KISQALI® (ribociclib succinate)

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC)

Presentation: Film-coated tablet containing ribociclib succinate, equivalent to 200 mg ribociclib. **Indication**: Early Breast Cancer: Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (see section 5.1 of the SmPC for selection criteria). In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist. Advanced or Metastatic Breast Cancer **:** 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. **Dosage and administration:** Early Breast Cancer: The recommended dose is 400 mg of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. In patients with early breast cancer, Kisqali should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur. When Kisqali is used in combination with an aromatase inhibitor (AI), the AI should be taken orally once daily continuously throughout the 28 day cycle. Please refer to the Summary of Product Characteristics (SmPC) of the AI for full information. In pre or perimenopausal women, or in men, the aromatase inhibitor should be combined with a LHRH agonist. Advanced or Metastatic Breast Cancer**:** The recommended dose is 600 mg once daily for 21 days, followed by 7 days off treatment, resulting in a complete cycle of 28 days. The treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. Kisqali should be used together with an aromatase inhibitor (AI) or with fulvestrant. The AI should be taken orally once daily continuously throughout the 28-day cycle. When Kisqali is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Refer to the SmPC of the AI or fulvestrant respectively for full information. Kisqali should be taken orally with or without food at the same time every day. **Dose modification:** Management of severe or intolerable adverse reactions (ARs) may require temporary dose interruption, reduction or discontinuation of Kisqali. For Early Breast Cancer and Advanced or Metastatic Breast Cancer dose reduction should be achieved by decrements of 200 mg daily. If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued. Complete blood counts (CBC) should be performed before and after initiating Kisqali 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. For neutropenia, no dose modifications required for grade 1 or 2. For grade 3, interrupt the dose until recovery to grade ≤2, then resume at same dose level. If toxicity recurs at grade 3, interrupt the dose until recovery to grade ≤2, then resume Kisqali and reduce by 1 dose level. For grade 3 febrile neutropenia interrupt the dose until recovery to grade ≤2, resume Kisqali and reduce by 1 dose level. For grade 4 interrupt the dose until recovery to grade ≤2, resume Kisqali and reduce by 1 dose level. Liver function tests (LFTs) should be performed before initiating Kisqali treatment, every 2 weeks for the first 2 cycles, then at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If grade ≥2 abnormalities are noted, more frequent monitoring is recommended. No dose adjustment is required for grade 1 abnormalities. For grade ≥2 abnormalities without a total bilirubin increase above 2x upper limit of normal (ULN) the following guidance applies: grade 2 where baseline grade is <2, dose interruption until recovery to ≤baseline grade then resume Kisqali at same dose, if grade 2 recurs then dose interrupt again then resume at next lower dose level. For grade 2 abnormalities where the baseline grade was equal to 2 no dose interruption is required. For grade 3 abnormalities dose interruption until recovery to ≤baseline grade, then resume Kisqali at next lower dose level. If grade 3 recurs then discontinue Kisqali. For grade 4 abnormalities discontinue Kisqali. For grade ≥2 abnormalities with a total bilirubin increase above 2x ULN, without cholestasis, discontinue Kisqali. ECG should be assessed before initiating treatment and repeated at approximately day 14 of the first cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended. Treatment with Kisqali should be initiated only in patients with QTcF values < 450 msec. In patients with QTcF >480 msec but ≤500 msec, the dose should be interrupted until QTcF resolves to <481 msec. Early Breast Cancer patients can then resume at the same dose. Patients with Advanced or Metastatic Breast Cancer should resume at the next lower dose. If QTcF ≥481 msec recurs, for both Early and Advanced or Metastatic Breast Cancer patients, interrupt treatment until QTcF resolves to <481 msec then then resume at next lower dose level. If the QTcF prolongation is >500 msec dose interruption of Kisqali until QTcF resolves to <481 msec, then resume at next lower dose level. If QTcF >500 msec recurs, discontinue Kisqali. If the QTcF is >500 msec or >60 msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali. Interstitial lung disease (ILD)/pneumonitis, Grade 1: no dose adjustment is required, initiate appropriate medical therapy and monitor as clinically indicated. Grade 2: Dose interruption until recovery to grade ≤1, then resume Kisqali at the next lower dose level. Grade 3 or 4: discontinue Kisqali. For other toxicities no dose adjustment required for grade 1 or 2, initiate appropriate medical therapy and monitor as clinically indicated. For grade 3, interrupt until recovery to grade ≤1, then resume Kisqali at the same dose. If grade 3 recurs, resume Kisqali at the next lower dose level. For grade 4, discontinue Kisqali. Concomitant use of strong CYP3A4 inhibitors should be avoided and an alternative concomitant medicinal product with less potential to inhibit CYP3A4 inhibition should be considered. If patients must be given a strong CYP3A4 inhibitor concomitantly with Kisqali, for patients taking 600mg, the dose should be reduced to 400mg. For patients on 400 mg Kisqali daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 200 mg. In patients who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of coadministration of a strong CYP3A4 inhibitor cannot be avoided, Kisqali treatment should be interrupted. These

recommended dose adjustments for Kisqali use with strong CYP3A4 inhibitors may not be optimal in all patients, for further information please refer to the SmPC. 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. In patients with Advanced or Metastatic Breast Cancer with mild hepatic impairment (Child Pugh class A) no dose adjustment required. In moderate (Child Pugh class B) and severe hepatic impairment (Child Pugh class C) patients can have increased (less than 2-fold) exposure to Kisqali and the starting dose of 400 mg Kisqali once daily is recommended. No dose adjustment is required for early breast cancer patients with hepatic impairment. *Elderly*: no dose adjustment is required for patients over the age of 65 *Paediatric population*: the safety and efficacy of Kisqali in patients aged below 18 has not been established. **Contraindications:** Hypersensitivity to the active substance or to peanut, soya or any other listed excipients. **Warnings/precautions:** Critical Visceral Disease: The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease. Neutropenia: Based on the severity of the neutropenia, Kisqali treatment may have to be interrupted, reduced or discontinued. Hepatobiliary toxicity: Liver function tests should be performed before and after initiating treatment with Kisqali. Based on the severity of the transaminase elevations, treatment with Kisqali may have to be interrupted, reduced or discontinued as advised in the SmPC. QT Interval prolongation: The use of Kisqali with medicinal products known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval. Kisqali should be avoided in patients with long QT syndrome, uncontrolled or significant cardiac disease and electrolyte abnormalities. Kisqali is not recommended for use in combination with tamoxifen. Appropriate monitoring of serum electrolytes should be performed before initiating treatment, at the beginning of the first 6 cycles, and then as clinically indicated. Toxic epidermal necrolysis (TEN) has been reported with Kisqali treatment. If signs and symptoms suggestive of severe cutaneous reactions appear, Kisqali should be discontinued immediately. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali. Interstitial lung disease (ILD)/Pneumonitis has been reported with Kisqali. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough and dyspnoea and dose modifications should be managed as per the SmPC. Based on the severity of the ILD/Pneumonitis, which may be fatal, Kisqali may require dose interruption, reduction or discontinuation. Blood creatinine increase: Kisqali may cause blood creatinine to increase. In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment. CYP3A4 substrates: Ribociclib is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose. 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. Renal impairment: The recommended starting dose of 200 mg for patients with severe renal impairment is estimated to result in approximately 45% lower exposure compared with the Advanced or Metastatic Breast Cancer starting dose (600mg) in patients with normal renal function. The efficacy at this starting dose has not been studied. Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity. 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. Soya lecithin: see Contraindications. **Interactions:** Ribociclib is primarily metabolised by CYP3A4. Medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of ribociclib. Co-administration of Kisqali with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products and other medicinal products that are known to prolong the QT interval should be avoided. Please refer to the SmPC for full information on the interactions with Kisqali. **Fertility, pregnancy and lactation**: Kisqali is not recommended during pregnancy and in women of childbearing potential not using contraception. Patients receiving Kisqali should not breast-feed for at least 21-days after the last dose. 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. **Effects on ability to drive and use machines:** Kisqali may have a minor influence on the ability to drive and use machinery; patients should be cautious in case they experience fatigue, dizziness or vertigo. **Undesirable effects in Early Breast Cancer:** *Very common:* Infections, neutropenia, leukopenia, headache, cough, nausea, diarrhoea, constipation, abdominal pain, alopecia, fatigue, asthenia, pyrexia, abnormal liver function tests. *Common:* Anaemia, thrombocytopenia, lymphopenia, hypocalcaemia, hypokalaemia, appetite decreased, dizziness, dyspnoea, interstitial lung disease (ILD) / pneumonitis, vomiting, stomatitis, hepatotoxicity, rash, pruritus, peripheral oedema, oropharyngeal pain, blood creatinine increased, electrocardiogram QT prolonged. *Uncommon*: febrile neutropenia. **Undesirable effects in Advanced or Metastatic Breast Cancer**: *Very common:* Infections, neutropenia, leukopenia, lymphopenia, anaemia, decreased appetite, headache, dizziness, dyspnoea, cough, nausea, diarrhoea, vomiting, constipation, abdominal pain, stomatitis, dyspepsia, alopecia, rash, pruritus, back pain, fatigue, peripheral oedema, pyrexia, asthenia, abnormal liver function tests. *Common:* thrombocytopenia, febrile neutropenia, hypocalcaemia, hypokalaemia, hypophosphataemia, dry eye, lacrimation increased, vertigo, syncope, interstitial lung disease/pneumonitis, dysgeusia, hepatotoxicity, dry skin, erythema, vitiligo, oropharyngeal pain, dry mouth, increased blood creatinine, electrocardiogram QT prolonged. *Rare*: Erythema multiforme. *Not known:* Toxic epidermal necrolysis. Consult the summary of product characteristics in relation to other adverse reactions. Basic NHS Cost: 21 tablets = £983.33, 42 tablets = £1,966.67, 63 tablets = £2,950.00. **MA Number:** PLGB 00101/1100 **Legal category:** POM. Further information is available from Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ, UK. Tel: 01276 692255.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PV tool at www.novartis.com/report or alternatively email medinfo.uk@novartis.com or call 01276 698370