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

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. 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.

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.
* 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 same 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 on at least 2 separate ECGs, 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 – 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 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

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.

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.

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 pomegranates or pomegranate juice and 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, pimozide, 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).

It is currently unknown whether Kisqali may reduce the effectiveness of systemically-acting hormonal contraceptives.

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.

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, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron) should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactation

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

Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman (see section 5.3).

For further information concerning pregnancy, lactation and fertility, 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 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 data from 898 patients; 568 of whom were exposed to ribociclib at the recommended 600 mg dose, using the proposed treatment regimen of 600 mg ribociclib (Days 1-21 of a 28-day cycle), and including 381 who received ribociclib in combination with letrozole 2.5 mg once daily.

The safety data reported below are based on the data from the phase III clinical study with a median duration of exposure to ribociclib plus letrozole of 13 months (58.1% patients exposed for ≥12 months.)

Dose reduction due to adverse events, regardless of causality, occurred in 44.6% of patients receiving Kisqali plus letrozole and permanent discontinuation was reported in 7.5% of patients.

The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥2%, respectively) for which the frequency for Kisqali plus letrozole exceeds the frequency for placebo plus letrozole were neutropenia, leukopenia, headache, back pain, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash and neutropenia, leukopenia, abnormal liver function test, lymphopenia, hypophosphataemia, vomiting, nausea, fatigue and back pain, respectively.

Tabulated list of adverse reactions

Adverse drug reactions from the phase III clinical study (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 (≥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 6 Adverse drug reactions observed in the phase III clinical study

Adverse drug reaction	**Frequency**
Infections and infestations	
Urinary tract infection	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, insomnia	Very common
Eye disorders	
Lacrimation increased, dry eye	Common
Cardiac disorders	
Syncope	Common
Respiratory, thoracic and mediastinal disorders	
Dyspnoea Epistaxis	Very common Common
Gastrointestinal disorders	
Nausea, diarrhoea, vomiting, constipation, stomatitis, abdominal pain Dysgeusia, dyspepsia	Very common Common
Hepatobiliary disorders	
Hepatotoxicity[1]	Common
Skin and subcutaneous tissue disorders	
Alopecia, rash[2], pruritus Erythema	Very common Common
Musculoskeletal and connective tissue disorders	
Back pain	Very common

General disorders and administration site conditions	
Fatigue, peripheral oedema, asthenia, pyrexia	Very common
Investigations	
Abnormal liver function tests[3] Blood creatinine increased, weight decreased, electrocardiogram QT prolonged	Very common Common
[1]Hepatotoxicity: hepatocellular injury, drug-induced liver injury, hepatotoxicity, hepatic failure (single non-fatal case), autoimmune hepatitis (single case). [2]Rash: rash, rash maculopapular. [3]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 (74.3%) and a grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 59.6% of patients receiving Kisqali and letrozole in the phase III study.

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 15 days in the ribociclib plus letrozole treatment group following treatment interruption and/or reduction and/or discontinuation. Febrile neutropenia was reported in about 1.5% of patients exposed to Kisqali in the phase III study. 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 (0.9%) (see sections 4.2 and 4.4).

Hepatobiliary toxicity
In the phase III clinical study, hepatobiliary toxicity events occurred in a higher proportion of patients in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (24.0% versus 13.6%, respectively), with more grade 3/4 adverse events reported in the patients treated with ribociclib plus letrozole (11.4% versus 3.6%, respectively). Increases in transaminases were observed. Grade 3 or 4 increases in ALT (10.2% versus 1.2%) and AST (6.9% versus 1.5%) were reported in the ribociclib 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 4 (1.2%) patients and all patients recovered to normal levels within 154 days after treatment with Kisqali was discontinued.

Dose interruptions and/or adjustments due to hepatotobiliary toxicity events were reported in 8.4% of ribociclib plus letrozole treated patients, primarily due to ALT increased (5.7%) and/or AST increased (4.5%). Discontinuation of treatment with Kisqali plus letrozole due to abnormal liver function tests or hepatotoxicity occurred in 3.0% and 0.6% of patients respectively (see sections 4.2 and 4.4).

In the phase III clinical study and a phase Ib study with ribociclib plus letrozole treatment, 83.8% (31/37) 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 57 days for the ribociclib plus letrozole treatment group. The median time to resolution (to normalisation or grade ≤2) was 24 days in the ribociclib plus letrozole group.

QT prolongation
In the phase III clinical study 7.5% of patients in the ribociclib plus letrozole arm and 2.4% in the placebo plus letrozole arm had at least one event of QT interval prolongation (including ECG QT prolonged and syncope). Review of ECG data (average of triplicate) showed 1 patient (0.3%) had >500 msec post-baseline QTcF value, and 9 patients (2.7%) 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 0.9% of ribociclib plus letrozole treated patients due to electrocardiogram QT prolonged and syncope.

A central analysis of ECG data (average of triplicate) showed 11 patients (3.3%) and 1 patient (0.3%) with at least one >480 msec post-baseline QTcF for the ribociclib plus letrozole arm and the placebo plus letrozole arm respectively. Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was 15 days 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 are no known 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 µM (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-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.

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.

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 267 patients treated with ribociclib at doses ranging from 50 to 1200 mg, including 193 patients treated with ribociclib 600 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF was 22.87 msec (90% CI: 21.6, 24.1) at the mean observed C_{max} at a steady-state C_{max} (2237 ng/ml) following administration at the recommended 600 mg dose (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. 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 Tumors (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 cutoff) is provided in Tables 7 and 8.

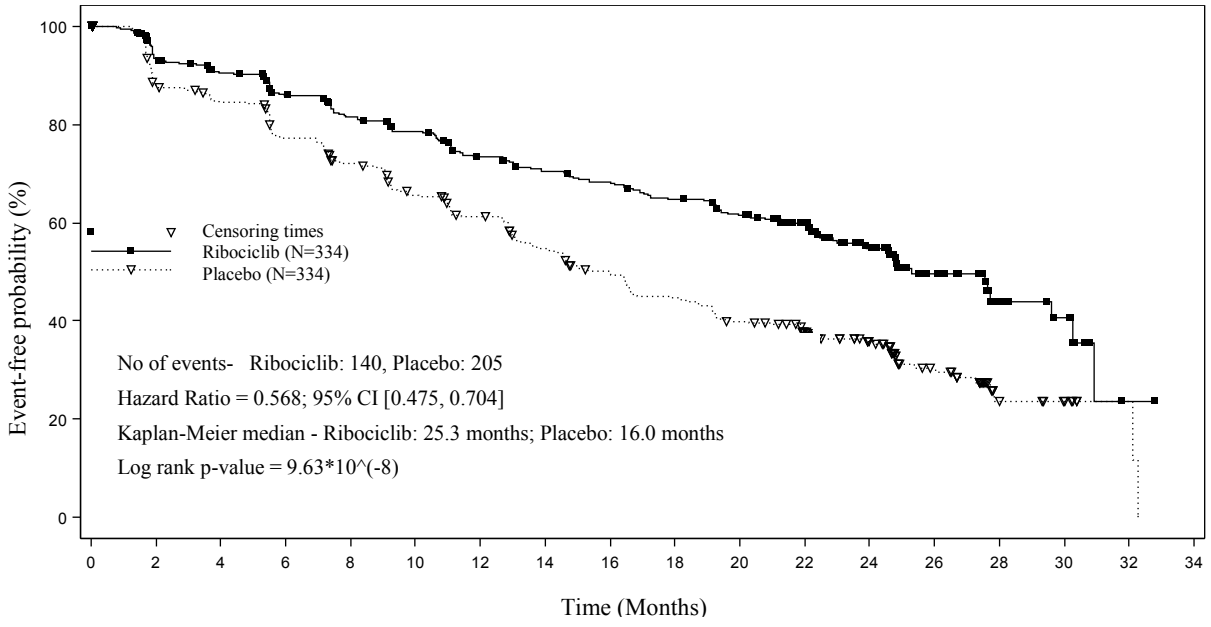
Median PFS was 25.3 months (95% CI: 23.0, 30.3) for ribociclib plus letrozole treated patients and 16.0 months (95% CI: 13.4, 18.2) for patients receiving placebo plus letrozole. 54.7% of patients receiving ribociclib plus letrozole were estimated to be progression-free at 24 months compared with 35.9% 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 Efficacy results – MONALEESA-2 primary efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cutoff)

	Updated analysis (02 January 2017 cutoff)	
	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 Kaplan-Meier plot of PFS based on investigator assessment – MONALEESA-2 (full analysis set 02 January 2017 cutoff)



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 ribociclib plus letrozole arm was observed in all individual patient subgroups of age, race, prior adjuvant or neo-adjuvant 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 ribociclib 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 cutoff)

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

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 (Vss/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 (≤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 m^2), 76 patients with mild renal impairment (eGFR 60 to <90 ml/min/1.73 m^2) and 35 patients with moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of ribociclib (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. 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.

Ribociclib has not been evaluated in fertility studies. However, chronic toxicity studies in rats and dogs revealed atrophic changes of the testes after histopathological evaluation. 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1221/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

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 postmenopausal women with a type of breast cancer called hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer that is advanced or has spread to other parts of the body (metastatic). It is used in combination with another type of medicine called an aromatase inhibitor.

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:
- 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 and rifampicin.
- 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.
- 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 pomegranates or drink grapefruit or pomegranate 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
You should only take Kisqali if you have already gone through the menopause.

Your doctor may request a negative pregnancy test before starting you on treatment with Kisqali.

Driving and using machines
Treatment with Kisqali may lead to tiredness. 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.
- Your doctor will tell you the dose of aromatase inhibitor that you should take in combination with Kisqali and when you should take it.

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). **Tell your doctor straight away if you get new or worsening symptoms.** *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). **Tell your doctor straight away if you get new or worsening symptoms.** *Very common (may affect more than 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). **Tell your doctor straight away if you get new or worsening symptoms**. *Common (may affect up to 1 in 10 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)
- 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)
- Difficulty falling asleep

Common (*may affect up to 1 in 10 people)*

- 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
- Nose bleeds

- Strange taste in the mouth (dysguesia)
- Upset stomach, indigestion, heartburn (dyspepsia)
- Abnormal kidney blood test result (high level of creatinine in the blood)
- Weight loss
- Skin reddening (erythema)

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