PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}KISQALI™

(ribociclib tablets)

200 mg ribociclib (as ribociclib succinate)

Protein kinase inhibitor, L01XE42

Anti-neoplastic agent

Novartis Pharmaceuticals Canada Inc.
385, Bouchard Blvd.
Dorval, Quebec, H9S 1A9

Date of Revision:
March 19, 2018

Control No: 203884

Table of Contents

[Pr]KISQALI™
(ribociclib tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	tablet 200 mg ribociclib (as ribociclib succinate)	No clinically relevant non-medicinal ingredients. *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING*

INDICATIONS AND CLINICAL USE

KISQALI™ (ribociclib tablets) is indicated:

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

Geriatrics (≥ 65 years of age):

Of 334 patients who received KISQALI plus letrozole in the pivotal phase III study, 150 patients (44.9%) were ≥ 65 years of age; no overall differences in safety or efficacy of KISQALI were observed between patients < 65 and ≥ 65 years of age.

Pediatrics (≤ 18 years of age):

There are limited data in pediatric patients and the safety and efficacy of KISQALI in this population have not been established.

CONTRAINDICATIONS

- Patients with hypersensitivity to this drug or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION and PACKAGING section.
- Patients with untreated congenital long QT syndrome, a QTcF interval of ≥450 msec at baseline, and those who are at significant risk of developing QTc prolongation (see WARNINGS and PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- QT interval prolongation (see WARNINGS AND PRECAUTIONS)
- Hepatotoxicity (see WARNINGS AND PRECAUTIONS)
- Neutropenia (see WARNINGS AND PRECAUTIONS)
- KISQALI (ribociclib tablets) should be administered by health professionals experienced with anti-cancer agents

Cardiovascular

QT interval prolongation

KISQALI has shown a concentration-dependent prolongation of the QTc interval, with the mean increase from baseline of approximately 19.6 msec (90% CI 18.0, 21.2) during steady-state treatment at 2 hours post-dosing on Day 15 in the phase III clinical trial (see ACTION AND CLINICAL PHARMACOLOGY section). One event of sudden death (0.3%) occurred during treatment with KISQALI plus letrozole in the phase III clinical trial in a patient with Grade 2 QT prolongation and Grade 3 hypokalemia. Syncope occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm versus 3 (0.9%) in the placebo plus letrozole arm. One patient (0.3%) had >500 msec post-baseline QTcF value, and 9 patients (2.7%) had a >60 msec QTcF interval increase from baseline in the phase III trial. In this trial, ECG assessments during steady-state were collected only on Cycle 1, Day 15.

QTc prolongation can lead to an increased risk of ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of Torsade de Pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, Torsade de Pointes can progress to ventricular fibrillation and sudden cardiac death.

Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following: female gender, age ≥ 65 years, baseline prolongation of the QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Treatment with KISQALI is contraindicated in patients with untreated congenital long QT syndrome; baseline prolongation of the QTc interval; and patients at risk of developing QTc prolongation (for example, uncontrolled, significant cardiac disease including but not limited to, recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias).Treatment with KISQALI should be avoided in patients with uncorrected

hypokalemia, hypomagnesemia, or hypocalcemia. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation or continuation of KISQALI treatment.

Particular care should be exercised when administering KISQALI to patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a QTc-prolonging drug.

Assess electrocardiography (ECG) before initiating KISQALI and repeat at approximately Day 14 of the first cycle, at the beginning of the second cycle, at regular intervals thereafter during steady-state treatment (at approximately Day 14 of the cycle), and whenever clinically indicated. QTc prolongation is expected to be maximal during days 8 – 21 of the 28-day cycle. Assess serum electrolytes prior to the initiation of KISQALI treatment, at regular intervals in later cycles, and whenever clinically indicated.

More frequent ECG and serum electrolyte monitoring may be required based on a patient's individual risk factors, and in the event of QTc prolongation and/or serum electrolyte imbalance (see Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION sections).

KISQALI should be avoided with other medicinal products known to prolong the QTc interval and/or strong CYP3A inhibitors as this may lead to further prolongation of the QTcF interval (see DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections). Use caution when KISQALI is in combination with agents known to cause bradycardia (e.g., beta-blockers, non-dyhydropyridine calcium channel blockers, clonidine, and digoxin.)

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6: Dose Modification and Management-QT prolongation (see DOSAGE AND ADMINISTRATION, ADVERSE DRUG REACTIONS and CLINICAL PHARMACOLOGY sections).

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heart beat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Thromboembolic events

In the pivotal phase III study, thromboembolic events occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm, compared with 3 (0.9%) in the placebo plus letrozole arm. Pulmonary embolism was reported in 4 patients (1.2%) receiving KISQALI plus letrozole and 1 patient (0.3%) receiving placebo plus letrozole.

Patients at risk of thromboembolic events should be closely monitored while receiving KISQALI.

Hematologic

Neutropenia

Neutropenia was the most frequently reported adverse drug reaction (74.3%) and a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 59.6% of patients receiving KISQALI plus letrozole in phase III clinical study.

Among the patients who had Grade 2, 3 or 4 neutropenia, the median time to Grade 2, 3 or 4 neutropenia was 16 days. The median time to resolution of grade ≥3 (to normalization or Grade <3) was 15 days in the KISQALI plus letrozole treatment group. Severity of neutropenia is concentration dependent. Febrile neutropenia was reported in 1.5% of patients exposed to KISQALI in the phase III clinical study. Physicians should inform patients to promptly report any fever (see ADVERSE DRUG REACTIONS section).

A complete blood count (CBC) should be performed before initiating therapy with KISQALI. CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4: Dose Modification and Management for Neutropenia (see DOSAGE AND ADMINISTRATION section).

Other Hematologic Parameters

Decreases in lymphocytes, leukocytes, hemoglobin and platelets were observed in patients treated with KISQALI plus letrozole. Grade 3 or 4 leukopenia was reported in 21% of patients in the KISQALI plus letrozole arm in the phase III study (see ADVERSE REACTIONS).

In clinical trials with KISQALI, anemia and leukopenia were usually managed with temporary KISQALI interruption and/or dose reduction. Monitor complete blood count prior to the start of KISQALI therapy, every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION sections).

Hepatic/Biliary

Hepatobiliary toxicity

In the phase III clinical study, increases in transaminases were observed. Grade 3 or 4 increases in alanine aminotransferase (ALT, 10.2% vs. 1.2%) and aspartate aminotransferase (AST, 6.9% vs. 1.5%) were reported in the KISQALI plus letrozole and placebo plus letrozole arms respectively.

Concurrent elevations of ALT or AST greater than three times the upper limit of normal (ULN) and of total bilirubin greater than two times the ULN, with normal ALP levels, and in the absence of cholestasis occurred in 4 (1.2%) patients, one with hepatic failure. All patients recovered to normal after discontinuation of KISQALI.

In the phase III clinical study and phase Ib study with KISQALI 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 (see ADVERSE REACTIONS section). The majority of increases in ALT and AST were reported without concurrent elevations of bilirubin. Among the patients who had Grade 3 or 4 ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI plus letrozole treatment group. The median time to resolution (to normalization or Grade ≤2) was 24 days in the KISQALI plus letrozole treatment group.

Liver function tests (LFTs) should be performed before initiating therapy with KISQALI. The LFTs should be monitored every 2 weeks for the first 2 cycles at the beginning of each of the subsequent 4 cycles, and as clinically indicated. In the event of Grade ≥ 2 LFT abnormality, more frequent monitoring is required (see Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION sections).

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5: Dose modification and management – Hepatobiliary toxicity (see DOSAGE AND ADMINISTRATION section). Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

Drug-Drug Interactions

Concomitant use of KISQALI and CYP3A inhibitors and inducers may respectively increase and decrease exposure to ribociclib. Co-administration of KISQALI and a strong CYP3A inhibitor or a strong CYP3A inducer should be avoided (see DRUG INTERACTION section).

Concomitant use of KISQALI and a CYP3A4 substrate may increase the exposure to the substrate. Co-administration of KISQALI and a CYP3A substrate with a narrow therapeutic index should be avoided; if avoidance is not possible, the dose of the substrate may need to be reduced (see DRUG INTERACTION section).

Sexual Function/Reproduction

Based on animal studies and the mechanism of action of ribociclib, KISQALI can cause fetal harm when administered to a pregnant woman. Women of reproductive potential should be advised to use effective contraception during therapy with KISQALI and for at least 21 days after the last dose (see TOXICOLOGY section).

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

Special Populations

Pregnant Women: There are no adequate and well-controlled studies using KISQALI in pregnant women. Ribociclib showed fetotoxicity and teratogenicity at doses which did not show maternal toxicity in rats and rabbits (see TOXICOLOGY section). It is possible that KISQALI can cause fetal harm when administered to a pregnant woman.

Female patients of reproductive potential should have a pregnancy test prior to initiation of treatment with KISQALI. The patient should be advised of the risk to a fetus, if KISQALI is used during pregnancy or if the patient becomes pregnant while taking KISQALI.

Nursing Women: Ribociclib and its metabolites readily passed into the milk of lactating rats. It is not known if ribociclib is excreted in human milk. There are no data on the effects of ribociclib on the breastfed child or the effects of ribociclib on milk production.

Because of the potential for serious adverse reactions in nursing infants from KISQALI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women taking KISQALI should not breastfeed for at least 21 days after the last dose (see TOXICOLOGY section).

Pediatrics (≤ 18 years of age): There are limited data in pediatric patients and the safety and efficacy of KISQALI in this population have not been established.

Geriatrics (≥ 65 years of age): Of 334 patients who received KISQALI in the phase III study (in ribociclib plus letrozole arm), 150 patients (44.9%) were ≥65 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and patients <65 years of age (see DOSAGE AND ADMINISTRATION section).

Hepatic insufficiency: Based on a pharmacokinetic trial in subjects with hepatic insufficiency (Child-Pugh Class), mild hepatic insufficiency (Child-Pugh Class A) had no effect on the exposure of ribociclib; no initial dose reduction is required for patients with mild hepatic insufficiency at baseline.

In the Phase III study, the efficacy and safety of KISQALI have not been studied in patients with moderate or severe hepatic impairment [defined as breast cancer patients with ALT or AST ≥ 5 x ULN or total serum bilirubin ≥ ULN (with the exception of documented Gilbert's Syndrome), as these patients were excluded according to the protocol eligibility criterion]. Treatment decision should be based on individual benefit/risk assessment for patients with moderate and severe hepatic insufficiency. If treatment is required, the starting dose should be reduced to 400 mg and patients should be closely monitored (see CLINICAL PHARMACOLOGY and DOSE AND ADMINISTRATION sections).

Renal insufficiency: In the Phase III study, the efficacy and safety of KISQALI have not been studied in patients with baseline serum creatinine >ULN per the protocol eligibility criteria. Treatment decision should be made based on individual benefit/risk assessment for patients with severe renal insufficiency. If treatment is required, patients should be closely monitored.

No dose adjustment is necessary for patients with mild or moderately impaired renal function and patients should be closely monitored (see CLINICAL PHARMACOLOGY and DOSE AND ADMINISTRATION sections).

Monitoring and Laboratory Tests

- Complete blood count (CBC): CBC should be performed before initiating therapy with KISQALI. CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles and as clinically indicated.

- Liver function test (LFT): LFT should be performed before initiating therapy with KISQALI. LFT should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated (for example, repeating liver enzyme and serum bilirubin twice weekly may be required in case of liver enzyme or bilirubin increase requiring dose interruption).

- Electrocardiography (ECG): Assess ECGs prior to initiating treatment, during Cycle 1 at approximately Day 14, at the beginning of Cycle 2, at regular intervals thereafter during steady-state treatment (at approximately Day 14 of the cycle), and whenever clinically indicated. Treatment with KISQALI should be initiated only in patients with QTcF value less than 450 msec. QTc prolongation is expected to be maximal during steady-state treatment between days 8 and 21 of the 28-day cycle. More frequent ECG monitoring is recommended whenever clinically indicated, for example in case of QTc prolongation during treatment or if the patient has underlying risk factors for Torsade de Pointes or is receiving concomitant treatment with drugs that prolong the QTc interval. Repeat ECGs should be performed if there are any symptoms that may be related to QT prolongation (e.g. palpitations or syncope), or in the event of electrolyte imbalances.
- Electrolytes: Monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed prior to initiation of treatment, at regular intervals during steady-state treatment in later cycles, and whenever clinically indicated. Any abnormality should be corrected before the initiation or continuation of KISQALI therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety evaluation of KISQALI is based on data from 898 patients; 568 of whom were exposed to KISQALI at the recommended 600 mg dose, using the proposed treatment regimen (Days 1-21 of a 28-day cycle), and including 381 patients who received KISQALI in combination with letrozole 2.5 mg daily dose.

The safety data reported below are based on the phase III clinical study of 668 enrolled (including 664 treated) postmenopausal women, randomized in a 1:1 ratio receiving KISQALI plus letrozole or placebo plus letrozole.

The median duration of exposure to KISQALI plus letrozole was 13 months with 58.1% patients exposed for ≥12 month.

The most common adverse drug reactions (ADRs) (reported at a frequency ≥20% and for which the rate for KISQALI plus letrozole exceeds the frequency for placebo plus letrozole) were neutropenia, leukopenia, headache, back pain, nausea, fatigue, diarrhea, vomiting, constipation, alopecia and rash.

The most common Grade 3/4 ADRs (reported at a frequency of ≥2% and for which the frequency for KISQALI plus letrozole exceeds the frequency for placebo plus letrozole) were neutropenia, leukopenia, abnormal liver function test, lymphopenia, hypophosphataemia, vomiting, nausea, fatigue, and back pain.

Dose reductions of KISQALI or placebo due to adverse events (AEs), regardless of causality occurred in 44.6% of patients receiving KISQALI plus letrozole and in 3.0% of patients receiving placebo plus letrozole. No dose reduction was allowed for letrozole in the phase III study. Permanent discontinuation of KISQALI or placebo due to AEs, regardless of causality occurred in 15.0% in the KISQALI plus letrozole arm versus 3.0% placebo plus letrozole arm; permanent discontinuations of KISQALI plus letrozole and placebo plus letrozole due to AEs were reported in 7.5% and 2.1% of patients in respective arms. The most common AEs leading to treatment discontinuation of both KISQALI and letrozole were ALT increased (2.7%), AST increased (2.4%) and vomiting (1.5%).

On-treatment deaths, regardless of causality, were reported in 3 (0.9%) patients treated with KISQALI plus letrozole versus 1 patient (0.3%) received placebo plus letrozole. Causes of death on KISQALI plus letrozole included one case of each of the following: study indication, death (cause unknown) and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation). There was one death due to the study indication on the placebo plus letrozole arm.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

ADRs from the phase III clinical study CLEE011A2301 (Table 1) are listed by MedDRA system organ class (MedDRA version 18.1) . 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.

Table 1 Adverse drug reactions observed in the phase III clinical study A2301

System Organ Class Adverse drug reactions	KISQALI plus Letrozole N=334 n (%) All grades	KISQALI plus Letrozole N=334 n (%) Grades 3/4	Placebo plus Letrozole N=330 n (%) All grades	Placebo plus Letrozole N=330 n (%) Grades 3/4
Blood and lymphatic system disorders				
Neutropenia	248 (74.3)	198 (59.3)	17 (5.2)	3 (0.9)
Leukopenia	110 (32.9)	70 (21.0)	13 (3.9)	2 (0.6)
Anaemia	63 (18.9)	4 (1.2)	15 (4.5)	4 (1.2)
Lymphopenia	35 (10.5)	23 (6.9)	7 (2.1)	3 (0.9)
Thrombocytopenia	30 (9.0)	2 (0.6)	2 (0.6)	0
Febrile neutropenia	5 (1.5)	4 (1.2)	0	0
Eye disorders				
Lacrimation increased	23 (6.9)	0	6 (1.8)	0
Dry eye	19 (5.7)	0	7 (2.1)	0
Cardiac disorders				
Syncope	9 (2.7)	6 (1.8)	3 (0.9)	2 (0.6)
Gastrointestional disorders				
Nausea	172 (51.5)	8 (2.4)	94 (28.5)	2 (0.6)
Diarrhea	117 (35.0)	4 (1.2)	73 (22.1)	3 (0.9)
Vomiting	98 (29.3)	12 (3.6)	51 (15.5)	3 (0.9)
Constipation	83 (24.9)	4 (1.2)	63 (19.1)	0
Stomatitis	41 (12.3)	1 (0.3)	22 (6.7)	0
Abdominal pain	35 (10.5)	4 (1.2)	25 (7.6)	0
Dysgeusia	31 (9.3)	1 (0.3)	19 (5.8)	0
Dyspepsia	22 (6.6)	0	14 (4.2)	0
General disorders and administration site conditions				
Fatigue	122 (36.5)	8 (2.4)	99 (30.0)	3 (0.9)
Peripheral edema	51 (15.3)	0	34 (10.3)	0
Asthenia	43 (12.9)	3 (0.9)	38 (11.5)	2 (0.6)
Pyrexia	42 (12.6)	1 (0.3)	18 (5.5)	0

System Organ Class Adverse drug reactions	KISQALI plus Letrozole N=334 n (%) All grades	KISQALI plus Letrozole N=334 n (%) Grades 3/4	Placebo plus Letrozole N=330 n (%) All grades	Placebo plus Letrozole N=330 n (%) Grades 3/4
Hepatic				
Hepatotoxicity[1]	5 (1.5)	5 (1.5)	1 (0.3)	0
Infections				
Urinary tract infection	44 (13.2)	2 (0.6)	28 (8.5)	0 (0.0)
Investigations				
Abnormal liver function tests[3]	60 (18.0)	32 (9.6)	18 (5.5)	8 (2.4)
Blood creatinine increased	23 (6.9)	2 (0.6)	3 (0.9)	0
Weight decreased	20 (6.0)	1 (0.3)	11 (3.3)	0
Electrocardiogram QT prolonged	15 (4.5)	1 (0.3)	4 (1.2)	0
Metabolism and nutrition disorders				
Decreased appetite	62 (18.6)	5 (1.5)	50 (15.2)	1 (0.3)
Hypocalcemia	18 (5.4)	5 (1.5)	6 (1.8)	0
Hypokalemia	15 (4.5)	4 (1.2)	10 (3.0)	3 (0.9)
Hypophosphatemia	14 (4.2)	12 (3.6)	3 (0.9)	2 (0.6)
Musculoskeletal and connective tissue disorders				
Back pain	66 (19.8)	7 (2.1)	58 (17.6)	1 (0.3)
Nervous system disorders				
Headache	74 (22.2)	1 (0.3)	63 (19.1)	1 (0.3)
Insomnia	39 (11.7)	1 (0.3)	31 (9.4)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	39 (11.7)	4 (1.2)	29 (8.8)	2 (0.6)
Epistaxis	15 (4.5)	0	6 (1.8)	0
Pulmonary embolism	4 (1.2)	3 (0.9)	1 (0.3)	1 (0.3)
Skin and subcautaneous tissue disorders				
Alopecia	111 (33.2)	0	51 (15.5)	0
Rash[2]	67 (20.1)	3 (0.9)	27 (8.2)	0

System Organ Class Adverse drug reactions	KISQALI plus Letrozole N=334 n (%) All grades	KISQALI plus Letrozole N=334 n (%) Grades 3/4	Placebo plus Letrozole N=330 n (%) All grades	Placebo plus Letrozole N=330 n (%) Grades 3/4
Pruritus	49 (14.7)	2 (0.6)	20 (6.1)	0
Erythema	17 (5.1)	0	4 (1.2)	0

[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.

Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III study. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Treatment discontinuation due to neutropenia occurred in 3 of 334 (0.9%) patients receiving KISQALI plus letrozole. Dose interruptions due to neutropenia occurred in 131 of 334 (39.2%) patients and led to dose reductions in 79 of 334 (23.7%) of the patients receiving KISQALI plus letrozole (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections).

Hepatobiliary toxicity

In the phase III clinical study, hepatobiliary toxicity events occurred in a higher proportion of patients in the KISQALI plus letrozole arm vs the placebo plus letrozole arm (24.0% vs 13.6%, respectively), with more Grade 3/4 adverse events reported in the patients treated with KISQALI plus letrozole (11.4% vs. 3.6%, respectively). Dose interruptions and/or adjustments due to hepatotobiliary toxicity events were reported in 8.4% of KISQALI 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 and hepatotoxicity were 3.0% and 0.6% respectively (see WARNINGS AND PRECAUTIONS section).

QT prolongation

In the phase III clinical study, 7.5% of patients in the KISQALI 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, syncope). Dose interruptions and/or adjustments were reported in 0.9% of KISQALI 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 post-baseline QTcF >480 m sec for the KISQALI plus letrozole arm and the placebo plus letrozole arms respectively. In this trial, ECG assessments during steady-state treatment were collected only on Cycle 1, Day 15. Among the patients who had QTcF prolongation of >480 msecs, the median time to onset was 15 days and these changes were reversible with dose interruption and/or dose reduction (see DOSAGE AND

ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY sections)

Abnormal Hematologic and Clinical Chemistry Findings

Clinically relevant abnormalities of routine hematological or biochemical laboratory values observed in the phase III clinical study are presented in Table 2.

Table 2 Laboratory abnormalities observed in the phase III clinical study

Laboratory abnormalities	**KISQALI plus Letrozole N=334 n (%) All grades**	**KISQALI plus Letrozole N= 334 n (%) Grades 3/4**	**Placebo plus Letrozole N=330 n (%) All grades**	**Placebo plus Letrozole N=330 n (%) Grades 3/4**
Leukocyte count decreased	311 (93.1)	115 (34.4)	97 (29.4)	5 (1.5)
Neutrophil count decreased	311 (93.1)	199 (59.6)	79 (23.9)	4 (1.2)
Hemoglobin decreased	189 (56.6)	6 (1.8)	87 (26.4)	4 (1.2)
Lymphocyte count decreased	169 (50.6)	45 (13.5)	74 (22.4)	13 (3.9)
Platelet count decreased	97 (29.0)	3 (0.9)	21 (6.4)	1 (0.3)
Alanine aminotransferase increased (ALT)	155 (46.4)	34 (10.2)	119 (36.1)	4 (1.2)
Aspartate aminotransferase increased (AST)	147 (44.0)	23 (6.9)	106 (32.1)	5 (1.5)
Creatinine increased	65 (19.5)	2 (0.6)	18 (5.5)	0
Phosphorous decreased	44 (13.2)	17 (5.1)	14 (4.2)	2 (0.6)
Potassium decreased	38 (11.4)	4 (1.2)	24 (7.3)	4 (1.2)
Bilirubin increased	17 (5.1)	4 (1.2)	9 (2.7)	1 (0.3)

DRUG INTERACTIONS

Overview

Ribociclib is primarily metabolized by CYP3A and is a time-dependent inhibitor of CYP3A *in vitro.* Therefore, medicinal products which can influence CYP3A enzyme activity may alter the pharmacokinetics of ribociclib and ribociclib can affect the pharmacokinetics of co-administered CYP3A substrates.

Drug-Drug Interactions

Drugs that may increase ribociclib plasma concentrations

CYP3A inhibitors: Co-administration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.21-fold. Concomitant use of strong CYP3A inhibitors including, but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole should be avoided. Alternative concomitant medications with low potential to inhibit CYP3A should be considered and patients should be monitored for ADRs *(*see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections).

If co-administration of KISQALI with a strong CYP3A inhibitor cannot be avoided, KISQALI dose should be reduced to 200 mg. However, there are no clinical data with this dose adjustment (see DOSAGE AND ADMINISTRATION). If the strong inhibitor is discontinued, the KISQALI dose should be resumed (after at least 5 half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability (see CLINICAL PHARMACOLOGY), the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ADRs is recommended. In the event of KISQALI related toxicity, dose interruption or reduction may be required until toxicity is resolved *(*see DOSAGE AND ADMINISTRATION section).

Patients should be instructed to avoid pomegranates or pomegranate juice, grapefruits or grapefruit juice, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib.

Drugs that may decrease ribociclib plasma concentrations

CYP3A inducers: Co-administration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89%. Avoid concomitant use of strong CYP3A inducers, including, but not limited to, phenytoin, rifampin, carbamazepine and St John's Wort *(Hypericum perforatum)*. An alternate concomitant medication with no or minimal potential to induce CYP3A should be considered (see WARNINGS AND PRECAUTIONS section).

Drugs that may have their plasma concentrations altered by ribociclib

CYP3A4 substrates: 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 PK (PBPK) 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 co-administration of KISQALI with a CYP3A substrates with a narrow therapeutic index should be avoided. If avoidance is not possible, the dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced.

CYP1A2 substrates: Co-administration of caffeine (CYP1A2 substrate) with multiple doses of KISQALI (400 mg) increased 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).

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

QTc interval prolongation has been reported in patients treated with KISQALI. The concomitant administration of KISQALI with other medicinal products known to prolong the QT interval or induce Torsade de Pointes should be avoided. While the patient is using KISQALI, other QTc-prolonging drugs should be discontinued and alternative concomitant drugs that do not prolong the QTc interval should be chosen. When it is not feasible to avoid concomitant use of drugs known to prolong the QTc interval, obtain ECGs and electrolytes prior to the start of treatment, after initiation of any drug known to prolong QTc interval, and monitor periodically as clinically indicated during treatment.

Drugs that have been associated with QTc interval prolongation and/or Torsade de Pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or Torsade de Pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., olanzapine, chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- anagrelide
- ivabradine
- 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Drugs that affect electrolytes

Use of KISQALI with drugs that can decrease electrolyte levels should be avoided to the extent possible. Such drugs include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; and proton pump inhibitors.

Drugs that reduce heart rate

Avoid using KISQALI concomitantly with drugs that reduce heart rate (e.g., beta-blockers, digitialis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, I_f inhibitors and sphingosine-1 phosphate receptor modulators).

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, inhibit CYP3A, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

Gastric pH elevating medications

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

Effect of ribociclib on transporters

Ribociclib may inhibit Breast Cancer Resistance Protein (BCRP), Organic Cation Transporter 2 (OCT2), Multidrug and Toxic Compound Extrusion Protein-1 (MATE1), and human Bile Salt Export Pump (BSEP) at clinically relevant concentrations. Patients should be closely monitored when co-administered with ribociclib and substrates of these transporters.

In vitro evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), Organic Anion Transporter 1 /3 (OAT1/3), Organic anion transporting polypeptides B1/B3 (OATP1B1/B3), Organic Cation Transporter 1 (OCT1), Multidrug and Toxic Compound Extrusion Protein 2K (MATE2K) and Multidrug resistance-associated protein 2 (MRP2) at clinically relevant concentrations.

Effect of transporters on ribociclib

Based on *in vitro* data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses.

Effect of ribociclib on CYP enzymes

In vitro, ribociclib did not inhibit CYP2E1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Ribociclib was a reversible inhibitor of CYP1A2 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5 at clinically relevant concentrations. No induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 was observed *in vitro* at clinically relevant concentrations.

Letrozole

Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs.

Drug-Food Interactions

KISQALI can be administered with or without food (see DOSAGE AND ADMINISTRATION).

Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI film-coated tablet with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12 (see CLINICAL PHARMACOLOGY section).

KISQALI should not be administered with grapefruit, grapefruit juice, or grapefruit-containing products or pomegranates, pomegranate juice, or pomegranate-containing products, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib.

Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4/5 that may decrease ribociclib plasma concentrations and should be avoided.

Drug-Laboratory Interactions

Interactions between KISQALI and laboratory tests have not been studied.

Drug-Lifestyle Interactions

Interactions between KISQALI and lifestyle have not been studied. However, fatigue and syncope have been reported with the use of KISQALI. Patients should exercise caution when driving or operating machinery while taking KISQALI.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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

Recommended dose

The recommended dose of KISQALI is 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. KISQALI can be taken with or without food (see CLINICAL PHARMACOLOGY and Drug-Food Interactions sections).

KISQALI should be co-administered with letrozole 2.5 mg taken once daily throughout the 28-day cycle. Refer to the Product Monograph of letrozole for the detailed condition of use.

Dose Adjustments for Adverse Drug Reactions

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, or permanent discontinuation of KISQALI. If dose reduction is required, the recommended dose reduction guidelines for adverse drug reactions (ADRs) are listed in Table 3.

Table 3 Recommended Dose Modification Guidelines for Adverse Drug Reactions

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

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

Tables 4, 5 and 6 summarize recommendations for dose interruption, reduction, or discontinuation of KISQALI in the management of specific ADRs. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS sections).

Table 4 Dose Modification and Management for Neutropenia

Neutropenia	**Grade 1 or 2** (ANC[1] 1,000/mm^3 – <LLN[2])	**Grade 3** (ANC[1] 500 - <1,000/mm^3)	**Grade 3 febrile* neutropenia**	**Grade 4** (ANC[1] <500/mm^3)
	No dose adjustment is required.	Interrupt KISQALI until recovery to Grade ≤2. Resume KISQALI at the same dose level. If toxicity recurs at Grade 3, interrupt KISQALI dose until recovery to grade ≤2 , then resume KISQALI at the next lower dose level.	Interrupt KISQALI until recovery of neutropenia to Grade ≤2. Resume KISQALI at the next lower dose level.	Interrupt KISQALI until recovery to Grade ≤2. Resume KISQALI at the next lower dose level.
	Perform Complete Blood Counts (CBC) before initiating treatment with KISQALI. After initiating treatment with KISQALI, monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated			

**Grade 3 neutropenia with a single episode of fever >38.3˚C (or) above 38˚C for more than one hour and/or concurrent infection*

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

[1]: absolute neutrophil count

[2]: lower limit of normal

Table 5 Dose Modification and Management for Hepatobiliary Toxicity

AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN	**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)**
	No dose adjustment is required.	Baseline at <Grade 2: Interrupt KISQALI until recovery to ≤ baseline grade, then resume KISQALI at same dose level. If Grade 2 recurs, resume KISQALI at next lower dose level. --- Baseline at Grade 2: No dose interruption.	Interrupt 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.			
Perform Liver Function Tests (LFTs) before initiating treatment with KISQALI. After initiating treatment with KISQALI, monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and monitor periodically as clinically indicated. If Grade ≥2 abnormalities are observed, more frequent monitoring, for example, twice weekly, is recommended.				
Baseline = prior to treatment initiation. *Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.*				

Table 6 Dose Modification and Management for QT Prolongation

ECGs with QTcF >480 msec	1. Interrupt the KISQALI dose 2. If QTcF prolongation resolves to <481 msec, resume KISQALI at the same dose level; 3. If QTcF ≥481 msec recurs, interrupt the KISQALI dose until QTcF resolves to <481 msec; and then resume KISQALI at next lower dose level
ECGs with QTcF >500 msec	If QTcF greater than 500 msec on at least 2 separate ECGs (within the same visit): Interrupt KISQALI until QTcF reaches <481 msec then resume KISQALI at next lower dose level.

Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Permanently discontinue KISQALI
Assess ECG prior to initiation of treatment. After initiating treatment with KISQALI, repeat ECGs on Day 14 or the first cycle, at the beginning of Cycle 2, at regular intervals thereafter during steady-state treatment (e.g., at approximately day 14 of the cycle), and whenever clinically indicated. Serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be assessed prior to initiation of treatment, at regular intervals in later cycles, and whenever clinically indicated with abnormalities corrected prior to commencement/ resumption of treatment.	

Table 7 Dose Modification and Management for 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.	Interrupt KISQALI dose 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, hepatobiliary toxicity, and QT interval prolongation.* *Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.*			

Dose modification for use of KISQALI with strong CYP3A inhibitors

Concomitant use of KISQALI should be avoided with strong CYP3A inhibitors and an alternative concomitant medication should be considered with low potential for CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, the KISQALI dose should be reduced to 200 mg once daily. If the strong inhibitor is discontinued, the KISQALI dose should be changed (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor *(*see WARNINGS AND PRECAUTIONS, INTERACTIONS section).

Special populations

Patients with hepatic insufficiency: Based on a hepatic impairment study in healthy subjects and non-cancer subjects with impaired hepatic function, no adjustment of the starting dose is necessary in patients with mild hepatic impairment (Child-Pugh class A).

A dose adjustment is required in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) and the starting dose of 400 mg is recommended (see CLINICAL PHARMACOLOGY section). However, in the Phase III trial, the efficacy and safety of KISQALI have not been studied in breast cancer patients with moderate and severe hepatic impairment; initiate KISQALI treatment in these patients only when perceived benefit outweighs potential risk.

Patients with renal insufficiency: No adjustment of the starting dose is necessary in patients with mild or moderate renal impairment. The pharmacokinetics of ribociclib in patients with

severe renal impairment (eGFR < 30 mL/min/1.73m^2) is unknown (see CLINICAL PHARMACOLOGY section); initiate KISQALI treatment in these patients only when perceived benefit outweighs potential risk.

Pediatrics (< 18 years of age): There are limited data in pediatric patients and the safety and efficacy of KISQALI in this population have not been established.

Geriatrics (≥ 65 years of age): No adjustment of the starting dose is required in patients over 65 years of age.

Missed Dose

If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Administration

KISQALI and letrozole should be taken approximately at the same time each day, preferably in the morning. KISQALI tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

OVERDOSAGE

Patients should be closely monitored for adverse drug reactions. General symptomatic and supportive measures, such as ECG monitoring, should be initiated in all cases of overdosage.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling 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) (see DETAILED PHARMACOLOGY, Pharmacodynamics section).

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 tumor regressions which correlated with inhibition of pRb phosphorylation at well tolerated doses.

In *in vivo* studies using patient-derived estrogen positive breast cancer xenograft models, combination of ribociclib and antiestrogens (i.e. letrozole) resulted in superior inhibition of tumor growth compared to each drug alone.

Pharmacodynamics

Cardiac electrophysiology

In the phase III clinical trial CLEE011A2301 and the phase Ib/II trial CLEE011X2107 in patients with HR+, HER2-negative breast cancer, ribociclib 600 mg was administered once daily for 21 consecutive days followed by 7-day planned break (28-day cycle, 3 weeks on/1 week off). QTcF interval prolongation occurred that was maximal during steady-state treatment (day 8-21) (Table 8).

Table 8 Mean QTc change from baseline observed in Studies CLEE011A2301 and CLEE011X2107

Study	Treatment	Cycle/Day	Time (h)	n	Mean Change from Baseline QTc (ms)	90% CI
CLEE011A2301	Ribociclib 600 mg + Letrozole 2.5 mg	C1/D15	0	308	13.5	12.1, 14.9
			2	277	19.6	18.0, 21.2
	Placebo + Letrozole 2.5 mg	C1/D15	0	313	1.7	0.5, 2.8
			2	307	1.8	0.7, 3.0
CLEE011X2107	Ribociclib 600 mg + Letrozole 2.5 mg	C1/D1	2	46	5.9	3.3, 8.6
			4	46	12.3	9.4, 15.3
		C1/D8	0	46	10.6	7.4, 13.7
			4	46	19.3	15.5, 23.1
		C1/D15	0	46	11.5	7.4, 15.6
			2	42	23.0	19.1, 26.9
			4	42	21.5	17.1, 25.9
			8	43	20.3	16.5, 24.1
		C1/D21	0	43	14.3	11.1, 17.5
			2	39	21.7	17.6, 25.8
			4	40	24.6	18.9, 30.3

Ribociclib also appears to decrease heart rate. In study CLEE011X2107 (Arm 1; N=47), the mean change from baseline in heart rate was -5.5 bpm (90% CI: -7.3, -3.7, n=42) at 2 h post-dosing on C1D15 and -7.1 bpm (90% CI -8.8, -5.3) at 2 h post-dosing on C1D21.

In study CLEE011A2301 (N=334), the mean change from baseline in heart rate on C1D15 at 2 h post-dose was -2.2 bpm (90% CI -3.2, -1.2; n=277) in the ribociclib plus letrozole arm and 1.7 bpm (90% CI: 0.8, 2.7, N=307) in the placebo plus letrozole arm.

Pharmacokinetics

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50 mg to 1,200 mg. Healthy subjects received single oral doses ranging of 400 or 600 mg or repeated daily oral doses (8 days) of 400 mg.

Table 9 Summary of Ribociclib's Pharmacokinetic Parameters

	C_{max} (ng/mL)	Tmax (h)	AUC0-24h (hr•ng/mL)	T1/2,acc (h)	CL/F (L/h)
Multiple doses (C1, D18/21) 600 mg (study X2101) Pooled[1]	n=57 1820 (62.4)	n=57 2.40 (0.683, 7.82)	n=54 23800 (66.0)	n=49 32.0 (63.2)	n=53 25.5 (65.7)
Multiple doses (C1 D21) 600 mg (study X2107)	n=28 1720 (44.6)	n=28 2.11 (1.05, 7.67)	n=23 23290 (52.2)	n=18 30.4 (38.7)	n=20 26.5 (53.2)

C: cycle; D: day; n: number of patients with cancer with corresponding evaluable PK parameters; PK: pharmacokinetics.

Data are presented as geometric mean (CV% geo mean) for all parameters except for Tmax which is presented as median (range)

[1] Pooled data from patients with cancer receiving intermittent schedule (3 weeks on 1 week off) and patients with cancer with continuous dosing (once daily for 28 days)

Absorption: Following oral administration of ribociclib to patients with advanced solid tumors or lymphomas peak plasma levels (C_{max}) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T_{max}). Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range tested (50 to 1,200 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: 0.972 to 6.40)

Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib film-coated tablet formulation with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12) (see Drug-Food Interaction section).

Distribution: Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000 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 1,090 L based on the population

pharmacokinetic analysis. In rats with intact blood brain barriers, there was relatively low brain penetration by ribociclib following oral administration and intracarotid injection.

Metabolism: *In vitro* and *in vivo* studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [^{14}C]ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation [dealkylation, C and/or N-oxygenation, oxidation (-2H)] and combinations thereof. Phase II conjugates of ribociclib phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (43.5%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9.39%, 8.60%, and 7.78% of total radioactivity, and 21.6%, 19.8%, and 17.9% of ribociclib exposure, respectively. The pharmacological effects of ribociclib are considered to be primarily due to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with the unchanged drug accounting for 17.3% and 12.1% in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts (≤ 2.78% of the administered dose).

Excretion: 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 half-life ($T_{1/2}$) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects.

Ribociclib is eliminated mainly via the feces, with a small contribution from 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 21 days; feces was the major route of excretion (69.1%), with 22.6% of the dose recovered in the urine.

Special Populations and Conditions

Pediatrics (< 18 years of age): There are limited data in pediatric patients and the pharmacokinetics of ribociclib in this population has not been established

Geriatrics (≥ 65 years of age): Population PK analysis did not show clinically meaningful effect of age on ribociclib PK parameters.

Effect of weight, gender and race: Population PK analysis showed that there are no clinically relevant effects of body weight, gender or race on ribociclib PK parameters.

Hepatic insufficiency: Based on a pharmacokinetic trial in subjects with hepatic impairment (Child-Pugh Class), mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in subjects 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

patients with normal hepatic function and 47 patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1 to ≤1.5 xULN and AST any value), mild hepatic impairment had no effect on the exposure of ribociclib.

Renal insufficiency: Based on a population pharmacokinetic analysis that included 77 patients with normal renal function [estimated glomerular filtration rate (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.

STORAGE AND STABILITY

KISQALI should not be stored above 30°C.

Store in original package to protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

KISQALI must be kept out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DOSAGE FORM: tablet.

COMPOSITION:

KISQALI (ribociclib tablets) is a light greyish violet film-coated tablet, unscored, round, curved with beveled edge, debossed with "RIC" on one side and "NVR" on the other side.

Medicinal ingredient: ribociclib succinate

Strength: Each tablet contains 200 mg ribociclib (as ribociclib succinate)

Excipients

Tablet core: Colloidal silicon dioxide; crospovidone (Type A); low-substituted hydroxypropylcellulose; magnesium stearate; microcrystalline cellulose;

Coating material: Iron oxide black (E172); iron oxide red (E172); lecithin (soy) (E322); polyvinyl alcohol (partially hydrolysed); talc; titanium dioxide (E171); xanthan gum.

PACKAGING:

KISQALI (ribociclib tablets) is supplied in unit dose blisters in the following pack sizes: 21, 42 and 63 tablets.

KISQALI TABLETS	
Package Size	Package Configuration
Pack of 63:	Blister pack containing 21 tablets (3 tablets for 600mg dose). 3 Blister packs per outer container
Pack of 42 :	Blister pack containing 14 tablets (2 tablets for 400 mg dose). 3 Blister packs per outer container
Pack of 21:	Blister pack containing 21 tablets (1 tablet for 200mg dose). 1 Blister pack per outer container

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common name: ribociclib succinate

Chemical name: Butanedioic acid—7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1)

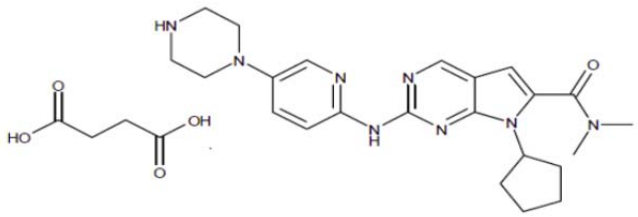
Molecular formula:

Free base: $C_{23}H_{30}N_8O$

Succinate salt: $C_{23}H_{30}N_8O \cdot C_4H_6O_4$

Molecular weight: 552.64 g/mole (salt form) [free base: 434.55 g/mol]

Structural formula:



Physicochemical properties:

Physical Description: Light yellow to yellowish brown crystalline powder

Solubility

The solubility of ribociclib succinate drug substance is pH-dependent, with high solubility in acidic media and low solubility in neutral media.

In acidic conditions, ribociclib succinate has a solubility > 2.4 mg/mL, but at pH 6.8 ribociclib freeform precipitates and the solubility decreases to 0.8 mg/mL. Ribociclib succinate is therefore considered to have low solubility according to the Biopharmaceutics Classification System (BCS).

pH: The pH of a 1.0% m/V solution of ribociclib succinate drug substance in water is 5.19.

pKa: The drug substance is an anhydrous succinate salt of ribociclib with pKa values of 5.3 and 8.5.

Partition Coefficient/Distribution Coefficient

Distribution coefficients were measured for ribociclib succinate drug substance at different pH at 37 °C. The different values as function of the pH are reported below.

Distribution coefficient

Media	pH (measured)	Distribution coefficient, D	Log D (measured)
n-octanol / pH 1 (0.1 N HCl)	0.93	0.00290	-2.57
n-octanol / pH 5.5 (acetate buffer)	5.57	0.471	-.033
n-octanol / pH 7.5 (phosphate buffer)	7.45	71.9	1.85

Melting point: Ribociclib succinate drug substance shows melting followed by decomposition at about 205 °C (by DSC).

CLINICAL TRIALS

Study CLEE011A2301

Study demographics and trial design

Table 10 - Summary of patient demographics for study CLEE011A2301

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender

LEE011 A2301	A randomized, double-blind, placebo-controlled, multicenter phase III clinical study in the treatment of postmenopausal women with HR positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone	Route of Administration : Oral Dosage: Ribociclib (600 mg once daily, on Days 1-21 of a 28-day cycle) plus letrozole (2.5 mg once daily in a 28-day cycle) Placebo (daily, on Days 1-21 of a 28-day cycle) plus letrozole (2.5 mg once daily in a 28-day cycle) Duration: Until disease progression, unacceptable toxicity, death, or study treatment discontinuation for any other reason. The median duration of exposure to the study treatment was similar in both treatment groups: 13.0 months in the ribociclib plus letrozole group (range: 0 to 23 months) and 12.4 months (range: 0 to 22 months) in the placebo plus letrozole group	A total of 668 patients with advanced breast cancer Ribociclib plus Letrozole: 334 female patients Placebo plus Letrozole: 330 female patients 4 patients in Placebo plus Letrozole never treated	Ribociclib plus letrozole Mean= 61.4 (23-91)years of age Placebo plus letrozole All patients 61.9 (29-88) years of age	Post-menopausal women

Study CLEE011A2301 was a randomized, double-blind, placebo-controlled, multicenter phase III clinical study of KISQALI plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with HR positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.

A total of 668 patients were randomized 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. 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 disease progression.

Patients enrolled in this study had a median age of 62 years (range 23 to 91) with 44.2% older than 65 years of age. The patients included were Caucasian (82.2%), Asians (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. A total of 43.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.8% had received antihormonal therapy in the neo/adjuvant setting prior to study entry. 34.1% of patients had *de novo* metastatic disease. 20.7% of patients had bone only disease and 59.0% of patients had visceral disease. Patients with CNS metastases documented at baseline were not permitted in this study.

The primary endpoint for the study was progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in the full population (all randomized patients). The median duration of study follow-up was 15.3 months.

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 (HR) = 0.556 with 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329], with an estimated 44% reduction in risk of progression for patients treated with the combination of reduction in KISQALI plus letrozole. The median PFS was not reached in the KISQALI plus letrozole arm [95% CI: 19.3 – not reached (NR)] at the time of primary analysis. The median PFS was 14.7 months (95% CI, 13.0, and 16.5) for placebo plus letrozole arm.

Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, bone only metastasis disease (Figure 2).

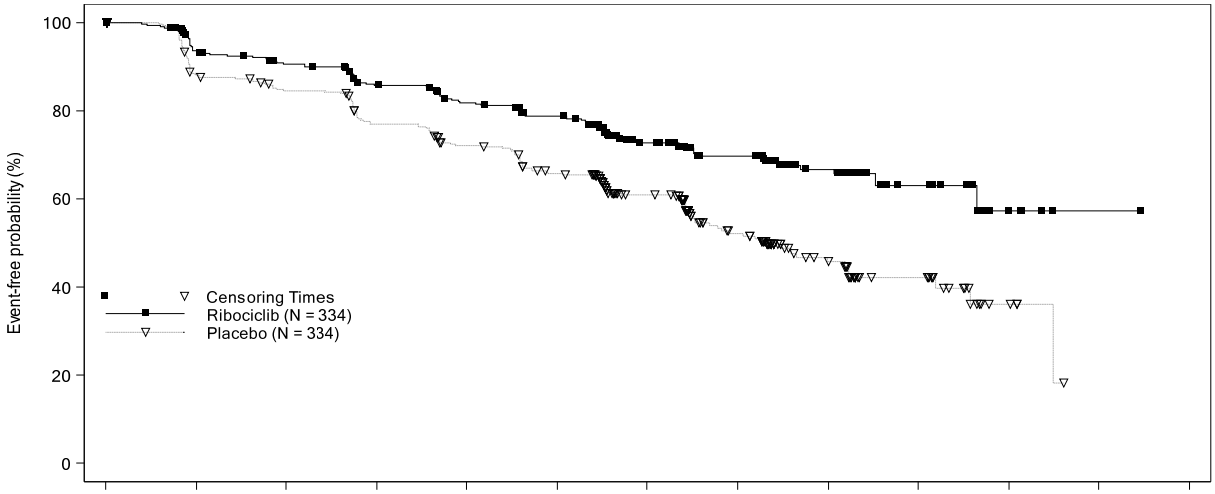
Progression free survival is summarized in Table 11 and the Kaplan-Meier curve for PFS is provided in Figure 1.

Table 11 CLEE011A2301 primary efficacy results - (PFS) based on Investigator assessment

	KISQALI plus letrozole N=334	**Placebo plus letrozole N=334**
Progression free survival		
Median PFS [months] (95% CI)	NR (19.3 – NR)	14.7 (13.0 – 16.5)
Hazard ratio (95% CI)	0.556 (0.429 to 0.720)	
p-value[a]	0.00000329	

CI=confidence interval; N=number of patients; NR = Not Reached.
[a] *p-value is obtained from the one-sided stratified log-rank test.*

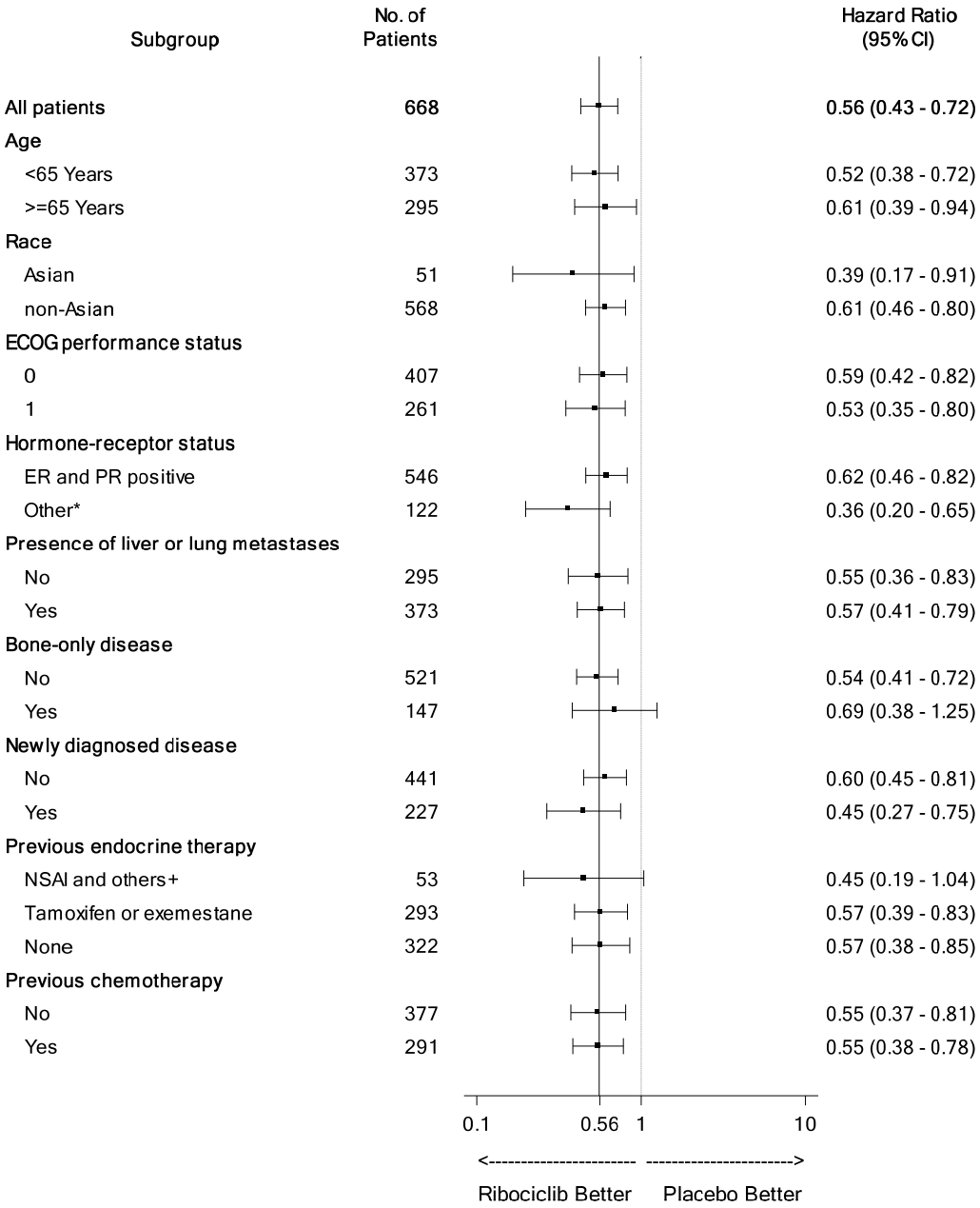
Figure 1 Kaplan-Meier plot of PFS based on Investigator review – Study A2301 (Full analysis set)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

Figure 2 Forest plot of Subgroup Analysis of PFS based on Investigator review – Study A2301 (Full analysis set)



**Other ER/PgR status refers to either ER+/PgR– or ER–/PgR+. +Patients in this group had not also received tamoxifen.*
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival; PgR, progesterone receptor.

Overall survival (OS) was a key secondary endpoint. At the time of primary PFS analysis, overall survival was not mature with 11% of events.

In patients with measurable disease, the overall response rate according to local radiologist assessment was 52.7% of patients (95% CI: 46.6%, 58.9%) in the KISQALI plus letrozole arm and 37.1% (95% CI: 31.1%, 43.2%) in the placebo plus letrozole arm.

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

Comparative Bioavailability Studies

Study A2103 was a randomized, open-label, single-center, crossover study to evaluate the BE of a new tablet formulation of ribociclib in comparison to a capsule formulation of ribociclib and the effect of food following a single oral dose of 600 mg in healthy subjects.

Table 12 Study A2103

Ribociclib
(3 x _200_ mg)
From measured data

Geometric Mean

Parameter	Test	Reference	Ratio of Geometric Means	90% Confidence Interval (Lower, Upper)
AUC_T (hr*ng/mL)	10600 n=31	10600 n=31	1	(0.881, 1.14)
AUC_I (hr*ng/mL)	10800 n=31	11500 n=30	0.937	(0.885, 0.991)
C_{MAX} (ng/mL)	601 n=31	596 n=31	1.01	(0.869, 1.17)
T_{MAX} (h)	3 n=31	3 n=31	0	(-4, 3)

Reference: 600mg LEE011 capsule, Test: 600mg LEE011 tablet.
- Model is a linear effects model of the log-transformed PK parameters. Included in the model were treatment, period and sequence as fixed effects and subjects nested within sequences as a random effect.
- n = number of subjects with non-missing values.
-AUC_T = AUClast
- The analysis is conducted on log transformed PK parameters. Then the results are back transformed to get adjusted geo-mean, Geo-mean ratio, and 90% CI.
- For Tmax, median is presented under 'Test' and 'Reference', median difference under 'Ratio of Geometric Means', and minimum and maximum differences under 90% CI.
- Source: Table 14.2-1.1a

DETAILED PHARMACOLOGY

Pharmacodynamics

In biochemical assays, ribociclib inhibits CDK4/Cyclin D1 and CDK6/Cyclin D3 enzyme complexes with IC50 values of 0.01 μM (4.3 ng/mL) and 0.039 μM (16.9 ng/mL), respectively. In a panel of serine/threonine and tyrosine kinases, inhibition of CDK4/D1 or CDK6/D3 was selective, ribociclib was inactive (IC50 >10 μM) against 34 other serine/threonine and tyrosine kinases and showing weak inhibition (> 2.0 μM) against Aurora A, HER1, and LCK with the IC50 values of 2.0 μM, 9.0 μM, and 7.7 μM, respectively, further demonstrating its relative inactivity against kinases other than CDK4/6.

Ribociclib was a potent inhibitor of cell proliferation in a wide variety of cancer cell lines. A functional pRb protein was a requirement for the inhibition of cell proliferation. Cancer cell lines with genetic aberrations in the CDK4/6 signalling pathways were particularly susceptible to the anti-proliferative effects of ribociclib. The IC_{50} value for cell proliferation inhibition by ribociclib in the mantle cell lymphoma cell line Jeko-2 with a translocation in the CCND1 gene (coding for cyclin D1) was 0.080 μM and the IC_{50} values for inhibition of phosphorylation of pRb and G1 arrest were 0.180 and 0.100 μM, respectively. The IC_{50} values for target phosphorylation of pRb, cell cycle assays and proliferation are similar and consistent with pRb phosphorylation tightly linked to G1 to S transition, with the inhibition of the pRb phosphorylation leading to G1 arrest in cells. The main mode inhibition of cell proliferation was growth arrest and there were no significant cell death. In Jeko-1 cells, the metabolites M4 (LEQ803) and M13 (CCI28) were less potent inhibitors than ribociclib, with G1 arrest occurring at IC50 values of >13 times that of ribociclib.

Ribociclib was tested in a panel of 47 breast cancer cell lines annotated with ER status. Luminal ER+ breast cancer cell lines were most sensitive to ribociclib, with 16 of the 18 cell lines with IC50s < 1 μM, while majority (21 out of 29) of the ER-negative cell lines have IC50s> 1 μM.

In immunocompromised mice with established MCF7 ER+ human breast cancer xenograft model, ribociclib monotherapy at 75 mg/kg p.o., once per day resulted in exposure approximately similar to 400 mg to 600 mg once daily in human. Ribociclib treatment resulted in tumor regression with minimal effect on body weight. In immunocompromised mice with a patient-derived ER+ breast cancer xenograft model (PDX191), ribociclib at 75 mg/kg/day exhibited tumor growth inhibition which correlated with inhibition of pRb phosphorylation.

The anti-tumor efficacy of ribociclib and letrozole was assessed in immunocompromised mice using a primary ER+ breast cancer xenograft model derived from a patient tumor with a known sensitivity to letrozole. Ribociclib at 75 mg/kg combined with letrozole at 2.5 mg/kg, both dosed orally every day for 55 days, induced greater tumor growth inhibition than each agent alone. The combination of ribociclib and letrozole demonstrated statistically significant antitumor activity with complete tumor growth inhibition, 2 out of 10 partial and 2 out of 10 complete tumor regressions. Tumor growth delay after stopping dosing was also observed.

Secondary Pharmacodynamics

Ribociclib and LEQ803 were assessed for their off-target activity on respectively 147 and 144 G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes.

For ribociclib, activities were found on phosphodiesterase PDE4d (IC50= 0.59 μM, n=2), rat vesicular monoamine transporter VMAT2 (IC50 = 6.3 μM, n=2), orexin-2 receptor (70% inhibition at 10 μM) and apelin receptor (54% inhibition at 10 μM). IC_{50} values were not determined for the last two mentioned targets.

For LEQ803, activities were found on phosphodiesterase PDE4d (IC50 = 0.6 μM), serotonin 5HT3 channel (IC50 = 2.63 μM), neuronal nicotinic alpha 2 channel (IC50 = 5.7 μM), cannabinoid CB1 receptor (IC50 = 28 μM), peripheral rat imidazoline I2 receptor (71% inhibition at 10 μM), rabbit monoamine transporter VMAT2 (84% inhibition at 10 μM) and rat brain sodium channel site II (70% inhibition at 10 μM). IC50 values were not determined for the last three mentioned targets.

The clinical free Cmax at the recommended dose of 600 mg ribociclib was 1.2 μM, and the free Cmax of LEQ803 was 0.03 μM.

Given the absence of brain penetration by ribociclib following oral administration and intracarotid injection in rats, centrally-mediated effects resulting from interactions with targets expressed in the central nervous system (VMAT-2, PDE4d, serotonin 5-HT3, rat brain sodium channel site II, neuronal nicotinic alpha 2 channel receptors, orexin receptor OX2 and cannabinoid CB1 receptors) are unlikely to develop in humans.

Safety pharmacology

Ribociclib caused a concentration-dependent decrease in hERG potassium channel currents in stably transfected HEK293 cells with an estimated IC50 of up to 53.0 μM.

Ribociclib caused a concentration-dependent inhibition of the Nav1.5 sodium channel currents in stably transfected HEK293 cells with an IC50 of 24 μM.
LEQ803, a major metabolite of ribociclib, caused a concentration-dependent suppression of hERG channel currents in stably transfected HEK293 cells with an IC50 of 4.5μM.

In vivo cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at exposures that would be expected to be achieved in patients following the recommended dose of 600 mg. Increased premature ventricular contractions (PVCs) were reported in a dog receiving a single oral dose of 100 mg/kg (resulting an exposure approximately 5-fold the clinical Cmax).

TOXICOLOGY

Repeated dose toxicity

The repeat dose toxicity was characterized in dogs and rats at doses up to and including maximum tolerated dose. In the dog, body weight loss, vomiting and severe liver/gall bladder toxicity occurred at 25 and 20 mg/kg/day in 2 and 4 week study. In the rat there were 2 potentially ribociclib related deaths in male rats after ≥17 weeks of dosing at 150 mg/kg/day. Both animals had irregular respiration and microscopically there were increased alveolar macrophage infiltrates.

Mild to moderate decreases in circulating red and white blood cells correlated with bone marrow hypocellularity and lymphoid tissue findings (atrophy/lymphoid depletion) in dogs and rats in studies ranging from 2 to 27 weeks in rats and 2 to 39 weeks in dogs. These changes as well as findings in intestinal mucosa (atrophy), skin (atrophy) and bone (decreased bone formation) in dog in the 2 and 4 week studies and are considered related to the pharmacological mechanism of action. They were reversible or partially reversible after 4 weeks without treatment.

Testicular changes with seminiferous tubule degeneration and secondary effects in the epididymis with reduced luminal sperm with luminal cellular debris and epithelial vacuolation were noted in rats and dogs. In the 15- and 27-week rat studies, the NOAEL was 25 mg/kg/day, while in the 15- and 39-week studies in the dog, a NOAEL was not identified (≤1 mg/kg/day). After a 4 week withdrawal period, the changes were consistent with partial recovery. The withdrawal period, given the length of the spermatogenic cycle, was not long enough for complete recovery.

Kidney changes, consisting of degeneration/regeneration of tubular epithelial cells, were noted in male rats only at ≥75 mg/kg/day in the 15 and 27 week studies. Vacuolation of bile duct epithelium was noted in males at 150 mg/kg/day after 4 and 15 weeks, in males at ≥75 mg/kg/day and in females at 300 mg/kg/day after 27 weeks of dosing. Increased incidence and severity of alveolar macrophage infiltrates in the lung of males at ≥75 mg/kg/day in the 4 week study, at 150 mg/kg/day in the 15 week study, and at ≥75 mg/kg/day in the 27 week study, as well as at 300 mg/kg/day in females in the 27 week study. The changes in kidney, bile duct and lung were reversible after a 4 week withdrawal period.

The pathogenesis of the bile duct toxicity, lymph node histiocytosis and lung macrophage infiltrates in the rat was suggested to be due to phospholipidosis. Liver/bile ducts/gallbladder was also identified as a target organ of toxicity for ribociclib in the dog. Findings in the dog included proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile and the proliferative changes within the intra- and extra-hepatic biliary tree may be indicative of irritation as a consequence of excretion of ribociclib and/or its metabolites via the biliary system. Mass balance data in rats and dogs show that the majority of ribociclib-related radioactivity is eliminated by metabolism via hepatic metabolism and biliary excretion.

The ribociclib exposures at the maximal feasible dose in repeat dose studies in rats and dogs were generally less than or similar to exposure in patients at MRHD. Thus, even for findings where NOAELs were identified, ribociclib exposure was less than clinical exposure at MRHD.

Reproductive toxicity/Fertility

Fertility has not been evaluated in dedicated toxicity study. However, the ribociclib general toxicology studies clearly identified the testes as a target tissue in rats and dogs (see Repeated Dose Toxicity) and reduced fertility or infertility is to be expected in males. There are no consistent histological indications of effects on female reproductive tract and the potential effect on female fertility is unknown.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1,000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 1,000 mg/kg/day was lethal in the maternal animals with embryofetal mortality. At 300 mg/kg/day, a slight, non-adverse trend towards reduced maternal body weight gain and fetal toxicity evidenced by reduced fetal weights accompanied by skeletal changes were considered to be transitory and/or related to the lower fetal weights. There were no effects upon embryo-fetal mortality or adverse effects on fetal morphology at 50 or 300 mg/kg/day. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was considered to be 300 mg/kg/day. The no-observed-effect-level (NOEL) for embryo-fetal development was considered to be 50 mg/kg/day.

In rabbits at doses of 30 and 60 mg/kg/day, there were adverse effects on embryo-fetal development as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal 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 13th ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-fetal mortality. The no-observed-effect level (NOEL) for maternal toxicity was 30 mg/kg/day and the NOEL for the embryo-fetal development was 10 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were lower than or at 1.5 times that achieved in patients at the highest recommended dose of 600 mg/day. Animal/human exposure margins at the no-effect doses for embryofetal toxicity in both species were well below therapeutic levels.

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56 fold higher in milk than in maternal plasma.

Genotoxicity

Ribociclib was not genotoxic *in vitro* in bacterial and mammalian cell assays with and without metabolic activation and in an *in vivo* study in rats.

Phototoxicity

Ribociclib was shown to absorb light in the UV-B and UV-A range. An *in vitro* phototoxicity test did not identify a relevant phototoxicity potential for ribociclib. The risk that ribociclib causes photosensitization in patients is considered low.

Carcinogenesis

No carcinogenesis studies have been conducted with ribociclib.

REFERENCES

1. Burris, HA *et al*. First-line Ribociclib + Letrozole In Patients With HR+, HER2– Advanced Breast Cancer Presenting With Visceral Metastases or Bone-only Disease: A Subgroup Analysis of the MONALEESA-2 Trial. Abstract presented at San Antonio Breast Cancer Symposium, December 6–10, 2016. Abst P4-22-16

2. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61-70. http://dx.doi.org/10.1038/nature11412

3. Herrera *et al* (2016) Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer; Cancer Research, Published OnlineFirst March 28,2016; DOl: 10.1158/0008-5472.CAN-15-0728

4. Hortobagyi G *et al* (2016) Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer NEJM N Engl J Med 2016; 375(18):1738-1748 November 3, 2016 DOI: 10.1056/NEJMoa1609709

5. Hosford SR and Miller TW(2014); Clinical potential of novel therapeutic targets in breast cancer: CDK4/6, Src, JAK/STAT, PARP, HDAC, and PI3K/AKT/mTOR pathways. *Pharmgenomics Pers Med* 2014;7:203–215. doi: 10.2147/PGPM.S52762

6. Infante JR *et al* (2016); A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas. Clin Cancer Res. 2016 Dec 1;22(23):5696-5705.

7. Juric *et al* (2016) Ribociclib (LEE011) and letrozole in estrogen receptor-positive (ER+), HER2-negative (HER2–) advanced breast cancer (aBC): Phase Ib safety, preliminary efficacy and molecular analysis. J Clin Oncol 34, 2016 (suppl; abstr 568)

8. Lange and Yee (2011) Killing the second messenger: targeting loss of cell cycle control in endocrine-resistant breast cancer. Endocr Relat Cancer; 2011:18(4):C19-24.

9. Miller, TW., Balko, JM., Fox EM, et al (2011) ER -Dependent E2F Transcription Can Mediate Resistance to Estrogen Deprivation in Human Breast Cancer ; Cancer Discovery 2011;1:338-351. Published OnlineFirst July 20, 2011(DOI: 10.1158/2159-8290.CD-11-0101).

10. O'Brien NA, Emmanuelle Di T, Raul A, et al (2014) In vivo efficacy of combined targeting of CDK 4/6, ER and PI3K signaling in ER+ breast cancer. Cancer Res;74 (19):4756.

11. O'Shaughnessy J *et al*; First-line Ribociclib + Letrozole in Patients With *De Novo* HR+, HER2– Advanced Breast Cancer: A Subgroup Analysis of the MONALEESA-2 Trial. Abstract Presented at San Antonio Breast Cancer Symposium, December 6–10, 2016. Abstract P4-22-05

12. Sonke, GS *et al.* (2017) Efficacy and safety of ribociclib (LEE011) + letrozole in elderly patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) in MONALEESA-2. Abstract presented at: 2017 European Cancer Congress; January 27-30, 2017; Amsterdam. Abstract 2LBA - See more at: http://www.onclive.com/web-exclusives/ribociclib-both-active-and-safe-in-elderly-patients-with-hrher2-breast-cancer#sthash.Fb14QRbT.dpuf

13. Zwijsen RML *et al* (1997) CDK-independent activation of estrogen receptor by cyclin D1. Cell; 88:405-15.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

KISQALI™
ribociclib tablets

Read this carefully before you start taking **KISQALI™** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KISQALI**.

Your breast cancer will be treated with **KISQALI** in combination with letrozole. Read the letrozole Patient Medication Information leaflet carefully as well as this one.

Serious Warnings and Precautions

KISQALI should only be administered by a healthcare professional experienced in the use of anti-cancer drugs.

The following serious side effects have been seen in people taking KISQALI:

- **Heart problems:** chest pain or discomfort,heart palpitations, fast or slow heartbeat, dizziness, lightheadedness, fainting, sudden death
- **Liver problems:** itching, yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite
- **Low levels of white blood cells:** fever, sore throat, mouth ulcers or other signs of infections

What is KISQALI used for?

KISQALI is used for the treatment of postmenopausal women with a certain type of breast cancer that is advanced and may not be able to be removed by surgery or has spread to other parts of the body. KISQALI is to be used in combination with another medicine for breast cancer, called letrozole.

How does KISQALI work?

KISQALI belongs to a family of medications called kinase inhibitors. These medications work by stopping cancer cells from dividing and growing.

KISQALI has to be used together with another anti-cancer medicine called letrozole. When given together with letrozole, KISQALI may slow down the growth and spread of breast cancer cells.

What are the ingredients in KISQALI?

Medicinal ingredients: ribociclib succinate

Non-medicinal ingredients: Colloidal silicon dioxide; crospovidone (Type A); iron oxide black (E172); iron oxide red (E172); lecithin (soy) (E322);low-substituted hydroxypropylcellulose; magnesium stearate; microcrystalline cellulose;polyvinyl alcohol (partially hydrolysed); talc; titanium dioxide (E171); xanthan gum.

What KISQALI looks like and contents of the pack

KISQALI is supplied in aluminum blister packs.

The tablet is light greyish violet, unscored, round, curved with beveled edges, debossed with "RIC" on one side and "NVR" on the other side

KISQALI comes in the following dosage forms:

Tablets; 200 mg ribociclib (as ribociclib succinate)

Do not use KISQALI if you:

- are allergic (hypersensitive) to ribociclib succinate or to any of the other ingredients of KISQALI.

- have serious heart problems including a condition known as "congenital long QT syndrome".

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KISQALI. Talk about any health conditions or problems you may have, including if you:

- have fever, sore throat or mouth ulcers due to infections (signs of low level of white blood cells).
- have or have ever had any problems with your liver.
- have or have ever had heart problems, such as an irregular heartbeat, rate or rhythm, or low levels of potassium, magnesium, calcium or phosphorous in your blood.
- have a family history of sudden cardiac death.
- are dehydrated, suffer from persistent vomiting or an eating disorder.
- have diabetes.
- have a condition called "autonomic neuropathy" that causes problems with blood pressure, heart rate, sweating, bowel and bladder control and digestion.
- are pregnant, think you might be pregnant, or are planning to have a baby. KISQALI may harm your unborn baby. If you are able to become pregnant, your healthcare professional will make sure that you are not pregnant before starting KISQALI. You must use effective birth

control during treatment and for at least 21 days after stopping KISQALI. Ask your healthcare professional about ways to avoid becoming pregnant.
- are breast-feeding or plan to breast-feed. You should not breastfeed while you are taking KISQALI or for 21 days after your last dose.
- are taking any medicines or supplements.

Other warnings you should know about:

Your healthcare professional will do blood tests and a test to see how well your heart is working, called an electrocardiogram (ECG), before you start taking KISQALI and at regular intervals during your treatment.

Driving and Using Machines: KISQALI can cause fatigue and fainting. You should use caution when driving or operating potentially dangerous machinery while you are taking KISQALI.

During your treatment with KISQALI, tell your healthcare professional straight away:

- If you have fever, chills, weakness and frequent infections with signs such as, sore throat or mouth ulcers. This could be due to a low level of white blood cells.
- If you have tiredness, itchiness, yellow skin, nausea, vomiting, yellowing of the whites of your eyes, loss of appetite, pain in the abdomen, dark or brown urine, or more than normal bleeding or bruising. These could be signs of problems with your liver.
- If you have chest pain or discomfort, changes in heart beat (faster or slower), palpitations, if your lips turn blue, if you feel lightheaded, dizzy or faint, if you have trouble breathing, or if your skin or your legs swell. These could be signs of problems with your heart.

Children and adolescents (under 18 years old)

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

Fertility in male patients

KISQALI may reduce fertility in male patients.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

The following may interact with KISQALI:

- Some medicines used to treat infections. These include medicines which treat fungal infections, such as ketoconazole, itraconazole, fluconazole, voriconazole, amphotericin B and posaconazole, or medicines which treat certain types of bacterial infections, such as telithromycin, clarithromycin, erythromycin, azithromycin, moxifloxacin, levofloxacin,

ciprofloxacin and pentamidine

- Some medicines used to treat malaria such as quinine and chloroquine
- 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, phenytoin, rifampin and midazolam
- St. John's Wort, an herbal product used to treat depression and other conditions (also known as *hypericum perforatum*)
- Some medicines used to treat heart rhythm problems such as amiodarone, disopyramide, procainamide, quinidine, sotalol, ibutilide, dronedarone, flecainide and propafenone
- Some medicines used to treat heart problems such as ivabradine, beta-blockers, digitialis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, I_f inhibitors and sphingosine-1 phosphate receptor modulators
- Some medicines used to treat high blood pressure such as verapamil and loop, thiazide and other diuretics ("water pills")
- Some medicines used to treat mental health problems such as olanzapine, chlorpromazine, pimozide, haloperidol, droperidol and ziprasidone
- Some medicines used to treat depression such as fluoxetine, citalopram, venlafaxine, amitriptyline, imipramine and maprotiline
- Some medicines used to treat migraines such as dihydroergotamine and ergotamine
- Some anesthetics used during surgery and pain medicines such as alfentanil, fentanyl and methadone
- Some medicines used to suppress the immune system in people who have had organ transplants such as cyclosporine, everolimus, sirolimus and tacrolimus
- Some medicines used to treat cancer such as ondansetron, sunitinib, nilotinib, ceritinib, vandetanib, arsenic trioxide and vorinostat
- Some medicines used to treat breathing problems, like asthma, such as salmeterol and formoterol
- Domperidone used to increase milk supply in breastfeeding mothers
- Anagrelide used to treat high levels of blood platelets
- Corticosteroids used to treat swelling and to suppress the immune system
- Proton Pump Inhibitors (PPIs) used to treat heartburn
- Laxatives and enemas
- Do not eat pomegranates, drink pomegranate juice, eat grapefruits or drink grapefruit juice while you are taking KISQALI.

You should also tell your healthcare professional if you are already taking KISQALI and you are prescribed a new medicine that you have not taken before.

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

How to take KISQALI:

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

Do not take more pills than the number prescribed by your healthcare professional.

You should not eat grapefruit or pomegranate or drink grapefruit or pomegranate juice while you are taking KISQALI. They may increase the amount of KISQALI in your blood and affect how KISQALI works.

- You should take KISQALI once daily, for 21 consecutive days. This is followed by 7 days off-treatment.
- Taking KISQALI at the **same time of day** will help you to remember when to take it. It is better to take KISQALI in the morning.
- KISQALI tablets should be **swallowed whole** (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be taken if it is broken, cracked, or otherwise not intact.
- KISQALI tablets can be taken with or without food.
- KISQALI tablets should be taken in combination with letrozole. Your healthcare professional will tell you exactly how many tablets of KISQALI to take and the dose of letrozole you should take and also when you should take it.

It is very important to follow your healthcare professional's advice. If you have certain side effects, your healthcare professional may ask you to take less medicine, to skip a dose or to stop treatment.

Usual starting dose:

600 mg orally (3 tablets of 200 mg) taken once daily for 21 consecutive days followed by 7 days off-treatment.

Continue taking KISQALI for as long as your healthcare professional tells you to. This is a long-term treatment, possibly lasting for months or years. Your healthcare professional will regularly monitor your condition to check that the treatment is working.

Overdose:

If you think you have taken too much KISQALI, or if someone else accidentally takes your medicine, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Show the KISQALI packet. Medical treatment may be necessary.

Missed Dose:

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

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

If you stop taking KISQALI:

Stopping your treatment with KISQALI may cause your condition to become worse. Do not stop taking KISQALI unless your healthcare professional tells you to stop.

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

What are possible side effects from using KISQALI?

These are not all the possible side effects you may feel when taking KISQALI. If you experience any side effects not listed here, contact your healthcare professional.

Some side effects are very common

- Reduced appetite
- Shortness of breath, labored breathing
- Back pain
- Nausea
- Diarrhea
- Vomiting
- Constipation
- Mouth sores or ulcers with gum inflammation
- Abdominal pain
- Hair loss or hair thinning
- Rash
- Itching
- Tiredness (fatigue)
- Weakness
- Fever
- Headache
- Difficulty falling asleep
- Swollen hands, ankles or feet (edema)

Some side effects are common

- Watering or tearing of eyes
- Dry eye
- Nose bleeds
- Strange taste in the mouth

- Upset stomach, indigestion
- Skin reddening
- Decreased weight

KISQALI can cause abnormal blood test results (such as an increase in creatinine or low levels of phosphate). Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Low levels of white blood cells:** fever, sore throat or mouth ulcers due to infections			√
Liver problems: itchiness, yellow skin, nausea, vomiting, yellowing of the whites of your eyes, loss of appetite, pain in the abdomen, dark or brown urine, or more than normal bleeding or bruising.			√
Anemia (low levels of red blood cells): fatigue, loss of energy, weakness, shortness of breath		√	
Urinary tract infection: pain and/or burning when urinating, blood in the urine, increased urge to urinate		√	
COMMON **Low levels of platelets:** spontaneous bleeding or bruising			√
Febrile neutropenia: sore throat or mouth ulcers with a single episode of fever >38.3°C (or) above 38°C for more than one hour and/or with infection			√
Low levels of potassium in the blood: irregular heartbeat, muscle weakness			√

Low levels of calcium in the blood: muscle cramps and spasms, numbness and tingling in the hands, feet and face			√
Fainting (syncope)			√
Heart problems: irregular heart beat (change in the electrical activity of the heart which may cause sudden death), chest pain or discomfort, dizziness, palpitations			√
UNCOMMON **Blood clot in the lung:** sudden, severe chest pain and trouble breathing, coughing up blood, rapid breathing and heartbeat			√
UNKNOWN FREQUENCY **Serious allergic reactions:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date, which is stated on the box.

- Do not store above 30°C. Store in the original packaging to protect from moisture.
- Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Ask your pharmacist how to dispose of medicines you no longer use.

If you want more information about KISQALI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://www.canada.ca/en/health-canada.html); the manufacturer's website (http://www.novartis.ca) or by calling 1-800-363-8883.

KISQALI is a trademark.

This leaflet was prepared by:
Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec
H9S 1A9

Last revised: March 19, 2018