

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209092Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209092
PDUFA Goal Date	April 29, 2017
OSE RCM #	2016-1970; 2016-1976
 Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Doris Auth, Pharm.D., Associate Director (Acting)
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 27, 2017
Subject	Review to determine if a REMS is necessary
 Established Name	Ribociclib
Trade Name	Kisqali
Name of Applicant	Novartis
Therapeutic Class	Cyclin Dependent Kinase 4/6 Inhibitor
Formulation(s)	200 mg tablets
Dosing Regimen	Recommended starting dose: 600 mg orally (3 x 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity ribociclib (Kisqali) is necessary to ensure the benefits of this product outweigh its risks. Novartis submitted a New Drug Application (NDA 209092) for ribociclib with the proposed indication as treatment 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 initial endocrine based therapy. The risks associated with the use of ribociclib are QT interval prolongation, hepatobiliary toxicity and neutropenia. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes warnings and precautions.

A REMS is not necessary to ensure the benefits outweigh the risks of ribociclib for the following reasons: a significant increase in rate of locally assessed PFS was demonstrated favorably with ribociclib plus letrozole arm. Despite the availability of hormone directed therapies for treatment of first-line HR-positive advanced breast cancer, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of advanced breast cancer to extend life, delay disease progression and/or lessen breast cancer related symptoms. The risk of QT interval prolongation, hepatobiliary toxicity and neutropenia and dose modifications to address safety will be communicated in labeling in the Warnings and Precautions section of the label.

DRISK and the Division of Oncology Products I (DOP I) agree that a REMS is not needed to ensure the benefits of ribociclib outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Kisqali (ribociclib) is necessary to ensure the benefits of this product outweigh its risks. Novartis submitted a New Drug Application (NDA) 209092 for ribociclib with the proposed indication as treatment 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 initial endocrine based therapy.¹ This application is under review in the DOP I. The applicant did not submit a REMS with this application but proposed labeling includes warnings and precautions and a contraindications.

2 Background

2.1 PRODUCT INFORMATION

Ribociclib, a new molecular entity, is an orally bioavailable, highly-selective, small-molecule inhibitor of cyclin-dependent kinase (CDK) 4 and 6; proposed for indication as treatment 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 initial

endocrine based therapy.² CDK 4 and CDK 6 are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation during phase G1 to phase S in the cell cycle. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb). By inhibiting CDK 4 and 6, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. The proposed starting dose of ribociclib is 600 mg orally (3 x 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Ribociclib is proposed to be coadministered with letrozole 2.5 mg taken once daily throughout the 28-day cycle. Patients are to continue the treatment until disease progression, unacceptable toxicity, death, or discontinuation from the treatment for any other reason.^a Ribociclib was granted a breakthrough therapy designation on June 3, 2016. Ribociclib is a new molecular entity (NME) NDA type 505(b)(1) pathway application.^b Ribociclib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for ribociclib (NDA 209092) relevant to this review:

- 05/31/2013: Investigation New Drug (IND) 117796 submission was received
- 05/01/2014: FDA agreed with the applicants initial pediatric study plan and acknowledged the request for a full waiver from PREA requirements in advanced breast cancer
- 08/02/2016: Breakthrough Therapy Designation request for ribociclib was granted for indication as treatment 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 initial endocrine based therapy
- 10/26/2016: The NDA 209092 was given Priority Review with PDUFA deadline of April 29th, 2017
- 07/21/2016: Applicant was informed at pre-NDA meeting that the determination of appropriate risk management strategies, particularly as it pertains to hepatotoxicity and QT prolongation, will be a review issue.
- 08/29/2016: NDA 209092 submission for ribociclib with the proposed indication as treatment 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 initial endocrine based therapy, received.
- 12/15/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ribociclib. The Applicant was also informed that there is the potential for PMR to study an alternative dosing regimen to mitigate this risk of

^a FDAAA factor (D): The expected or actual duration of treatment with the drug.

^b FDAAA factor (F): Whether the drug is a new molecular entity.

QT prolongation and second PMR to evaluate the dose for patients with severe renal impairment.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Breast cancer is the second leading cause of cancer death in women.^c The chance that a woman will die from breast cancer is about 1 in 36 (about 3%). The American Cancer Society estimates that approximately 252,710 new cases of invasive breast cancer will be diagnosed in women in United States^d and about 40,610 women will die from breast cancer in 2017.³ Breast cancer is a molecularly diverse disease with several clearly defined molecular subgroups.⁴ Clinically, however, three therapeutic groups are used: those classified as hormone receptor-positive, those classified as HER2-positive, and those classified as triple-negative. The predominant subset is HR-positive, HER2-negative disease. Of the new breast cancer cases diagnosed worldwide each year, roughly 60% to 65% are HR-positive, 20% to 25% are HER2-positive, and 15% to 18% are triple-negative.⁵ The expression profile of biological markers in breast cancer is correlated with prognosis and response to treatment, and therefore plays an important role in treatment decisions.⁶

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment of patients with advanced breast cancer (locally advanced not amenable to curative treatment and metastatic disease) is palliative in nature.⁷ In postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer, hormonal therapies are used prior to chemotherapies provided there is no visceral crisis. First-line endocrine agents for postmenopausal women include selective non-steroidal aromatase inhibitors (NSAIs) (letrozole and anastrozole, used interchangeably), steroidal aromatase inhibitors (exemestane), and selective estrogen receptor modulators (tamoxifen)^{8,9} (as shown in Table 1). Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone receptor positive, HER2-negative metastatic breast cancer.⁹ Many patients continue to develop resistance to NSAIs. Extensive nonclinical work suggested that cotargeting the CDK4/cyclin D1/Rb pathway and ER signaling by adding ribociclib to standard endocrine therapy may provide therapeutic benefit relative to endocrine therapy alone by enhancing the efficacy of endocrine therapy (by preventing acquired resistance from developing via the blockade of these specific pathways) and/or by reversing the resistance to endocrine therapy.^{2,5}

^c FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

^d FDAAA factor (A): The estimated size of the population likely to use the drug involved.

Table 1: Summary of Treatment Options Relevant to Proposed Indication

Trade Name (Generic)	Approved year	Indication	Dosing/ Administration	Warnings and Precautions	REMS
Selective inhibitor of cyclin-dependent kinases (CDKs) 4 and 6					
Ibrance ¹⁰ (Palbociclib)	2016	Indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.	125 mg once daily taken with food for 21 days followed by 7 days off treatment	Neutropenia, infection, embryo-fetal toxicity	No REMS
Non-Steroidal aromatase inhibitors					
Femara ¹¹ (Letrozole)	1997	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	2.5mg daily by mouth	Bone mineral density decrease, hot flashes, and arthralgias	No REMS
Arimidex ¹² (Anastrozole)	1995	First-line treatment of postmenopausal women with HRpositive or unknown locally advanced or metastatic breast cancer	1mg daily by mouth	Bone mineral density decrease, hot flashes, and arthralgias	No REMS
Steroidal aromatase inhibitors					
Aromasin ¹³ (Exemestane)	1999	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following	25mg daily by mouth	Bone mineral density decrease, hot flashes, and arthralgias	No REMS
Selective estrogen receptor modulator					
Soltamox ¹⁴ (Tamoxifen)	1977	In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.	20mg daily by mouth	Black Box Warning for Uterine malignancies, stroke and pulmonary embolism. The most frequent adverse reaction to tamoxifen is hot flashes.	No REMS

See the section 8 of this review for information regarding other oncology drugs that have AEs that are similar to those associated with ribociclib.

4 Benefit Assessment

The pivotal trial, MONALEESA-2 (study A2301) supporting this application consisted of a randomized, double-blind, placebo controlled, multicenter study which evaluated the combination of ribociclib plus letrozole versus placebo plus letrozole conducted in 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 to receive either ribociclib and letrozole (n= 334) or placebo and letrozole (n= 334), stratified according to the presence of liver and/or lung metastases. Letrozole 2.5 mg was given orally once daily for 28 days, with either ribociclib 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off.

The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The efficacy results from Study A2301 are summarized in Table 2.^{e,15} Study A2301 met its primary end point: the median duration of progression-free survival was not reached in the ribociclib group (95% CI, 19.3 to not reached) versus 14.7 months (95% CI, 13.0 to 16.5) in the placebo group (hazard ratio (HR), 0.56; 95% CI, 0.43 to 0.72; P = 3.29×10⁻⁶ for superiority). The rate of locally assessed progression-free survival was significantly higher in the ribociclib group than in the placebo group.^{f, 16} The Sponsor also provided a 90 day safety update (22 June 2016 cutoff) in which the HR for the primary endpoint was 0.559 (95% CI 0.443, 0.706), with a median PFS 22.4 months (95% CI 20.8, NE) in the ribociclib plus letrozole arm and 15.3 months (95% CI 13.0, 16.5) for the placebo plus letrozole arm. The improvement in PFS is clinically meaningful and represents a large improvement over current therapy. A Blinded Independent Central Review (BICR) analysis supported the primary endpoint of PFS.^{f, 16}

Table 2: Primary Analysis Results (PFS by investigator) at Interim Analysis

	Ribociclib +letrozole	Placebo + letrozole
Progression-free survival	N = 334	N = 334
Events (%)	93 (27.8)	150 (44.9)
Median (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		< 0.0001 ^a
Overall Response Rate	N=256	N=245
Patients with measurable disease (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)

^a p-value estimated from one-sided log-rank test
NR = not reached

The key secondary end point was overall survival. Other secondary end points included the overall response rate. The overall response rate in patients with measurable disease as assessed by the investigators was 52.7% (95% CI: 46.6%, 58.9%) in ribociclib plus letrozole and was 37.1% (95% CI: 31.1%, 43.2%) in the placebo plus letrozole arm.¹⁶ At the time of interim PFS analysis, 6.5% of patients had died, and overall survival data were immature. Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease.

^e Efficacy table and figure excerpted from the draft labeling, as currently edited by the FDA dated January 20, 2016.

^f FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

5 Risk Assessment & Safe-Use Conditions

The overall safety evaluation of ribociclib is based on data from 964 patients (industry-sponsored clinical studies) with the original NDA submission, August 29, 2016. The clinical safety data supporting this NDA is primarily derived from the Phase 3 registration Study A2301 (also referred to as MONALEESA-2) which enrolled 664 subjects (334 patients in the ribociclib plus letrozole arm, and 330 in the placebo plus letrozole arm). In MONALEESA-2, the most frequently reported treatment adverse events (TEAEs) (i.e., ≥10% of patients) in the ribociclib plus letrozole arm were neutropenia (60.8%), nausea (51.2%), fatigue (35.9%), diarrhea (35.0%), alopecia (33.2), vomiting (29.3), and arthralgia (27.2%). The most frequently reported TEAEs in the letrozole alone arm were fatigue (30.3%), arthralgia (28.8%), and nausea (28.5%). All adverse events (AEs) and serious adverse events (SAEs) were coded according to Medical Dictionary for Regulatory Activities (MedDRA). AEs were summarized by MedDRA primary system organ class (SOC), and by Preferred term (PT). In the Summary of Clinical Safety (page 11), the Sponsor noted that preferred terms were combined as follows: neutropenia (inclusive of granulocytopenia, neutropenia, and neutrophil count decreased); leukopenia (inclusive of leukopenia and white blood cell count decreased).¹⁷

Key safety findings from MONALEESA-2, and from the supportive safety database:

Deaths:

There were 4 deaths (3 in the ribociclib plus letrozole group and 1 in the placebo plus letrozole group) during treatment. One subject in each group died from progression of breast cancer. The remaining 2 deaths in the ribociclib group, one death was attributed to sudden death and the second death from unknown cause. The patient who was attributed to sudden death was known to be on concomitant methadone during treatment with ribociclib, though methadone was discontinued three weeks before the sudden death.

Grade 3 and 4 Adverse Reactions:

At the preferred term level, the most common grade 3-4 adverse events in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm were neutropenia (48.2% vs. 0.6%), neutrophil count decreased (14.1% vs. 0.3%), and white blood cell count decreased (12.9% vs. 0.3%). No grade 5 adverse events were noted.

Serious Adverse Events (SAEs), Discontinuations and Dose Modifications:

SAEs were more common in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (21.3 vs. 11.8%). The most common SAEs (all grades) in the ribociclib plus letrozole group were vomiting and abdominal pain (both 1.5%) compared to the placebo plus letrozole arm (0.6% and 0% respectively). Treatment-emergent adverse events leading to drug discontinuation were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (15.0% vs. 3.0%, any grade). The most common TEAEs (any grade, >1% incidence) in the ribociclib plus letrozole arm requiring dose discontinuation were increased ALT, increased AST, and vomiting. Treatment-emergent adverse events leading to drug interruption were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (71.3% vs. 14.8%, any grade). The most common TEAEs (any grade,

>5% incidence) in the ribociclib plus letrozole arm requiring dose interruption were neutropenia, decreased neutrophil count, vomiting, nausea, increased ALT, and decreased WBC.

QT prolongation, hepatobiliary toxicity and neutropenia are serious risks observed in patients treated with ribociclib. QT prolongation has been the safety signal of most concern during the review. These risks are discussed below.

QT Interval Prolongation:

QT interval prolongation AEs were more frequently reported in the ribociclib plus letrozole group compared with the placebo plus letrozole group (7.8% vs. 2.4%), with more grade 3/4 events reported in the patients treated with ribociclib plus letrozole (2.4% vs. 0.6%, respectively). The most frequent AEs reported in ribociclib plus letrozole group compared to placebo plus letrozole were electrocardiogram QT prolonged (4.5% vs 1.2%) and syncope (2.7% vs 0.9%).¹⁶ There were no reported cases of Torsade de Pointes.

Of the nine cases of syncope in the ribociclib plus letrozole group, five occurred at 600 mg, three occurred at 400 mg, and one occurred 8 cycles after stopping ribociclib. Drug interruption/reduction was required for 0.9% of ribociclib plus letrozole group secondary to ECG QT prolonged and syncope. Discontinuation of treatment with ribociclib plus letrozole due to QT interval prolongation occurred only in one patient (0.3%), who experienced sudden death. The patient was known to be on concomitant methadone during treatment with ribociclib, though methadone was discontinued three weeks before death.

A consult was requested for Interdisciplinary Review Team for QT studies.¹⁸ The review team stated that Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20 ms at 600 mg once daily dose. In Study A2301 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value, and nine patients out of 329 patients (2.7%) had a >60 msec increase from baseline in QTcF intervals. These ECG changes occurred within the first 15 days of treatment and were reversible with dose interruption.¹⁸ The finding supports the dose modification plan to manage QT risks in the label.

Hepatotoxicity:

Increases in transaminases were observed in Study A2301. Grade 3 or 4 increases in ALT (10% versus 1%) and AST (7% versus 2%) were reported in the KISQALI and placebo arms, respectively. Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI plus letrozole treatment group. The median time to resolution to Grade ≤ 2 was 24 days in the KISQALI plus letrozole treatment group.

Clinical reviewer stated that hepatobiliary toxicity was a substantial cause of Grade 3 and 4 toxicity among patients receiving ribociclib plus letrozole. Four patients (1.2%) in the ribociclib plus letrozole group met the biochemical definition of Hy's law; three cases were related to study treatment and none resulted in death. Clinical reviewer concluded that no meaningful conclusion can be drawn on the

exposure-response relationship for hepatobiliary toxicity because of low number of patients with LFT events and concomitant exposure data. The risk of hepaticotoxicity will be communicated in the Warnings and Precautions in label.

Neutropenia:

In Study A2301, neutropenia AEs occurred in a higher proportion of patients in the ribociclib plus letrozole group (n=249, 74.6%) compared with the placebo plus letrozole group (n=17, 5.2%). Grade 3 or 4 grouped neutropenia events occurred in 199 patients (59.6%). There were 6 reported febrile neutropenia events in 5 patients (1.5%) who received ribociclib plus letrozole; all events were noted by the Investigators to be related to study treatment. Four patients required a dose reduction and/or drug interruption. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 15 days in the KISQALI plus letrozole treatment group. Treatment discontinuation due to neutropenia was 0.9%.

Clinical reviewer stated that simulation results suggested lowering dose/exposure might lead to slightly lower neutropenia risks. This finding supports the proposed dose modification plans for the neutropenia management in the label.

6 Expected Postmarket Use

The proposed indication is as treatment 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 initial endocrine based therapy. It is expected that oncologists will be the primary health care provider to prescribe ribociclib and the use will be primarily in and out patient setting.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for ribociclib beyond routine pharmacovigilance and labeling. They do propose a Patient Information as part of labeling to inform patients regarding the potential risk of QT prolongation, hepaticotoxicity, and neutropenia.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for ribociclib, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and prescribing population.

Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of ribociclib in combination with an aromatase inhibitor^g as initial endocrine-based therapy for

^g Indication statement is updated in response to FDA's email of December 20, 2016: "update the PI to include your proposal for incorporating a more general class of hormonal therapy".

the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.¹⁶ Both interim and 90-day safety update analysis supports that ribociclib in combination with letrozole was shown to be efficacious by meeting its primary endpoint of PFS. Despite the availability of hormone directed therapies for treatment of first-line HR-positive advanced breast cancer, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies.^{5,16} In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of advanced breast cancer to extend life, delay disease progression and/or lessen breast cancer related symptoms and therefore ribociclib has the potential to fill this need in postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

The most concerning adverse reactions associated with the use of ribociclib are QT interval prolongation, hepatobiliary toxicity and neutropenia. These adverse events were considered concentration-dependant and reversible.

There are a number of oncology products that prolong QT interval. Caprelsa (vandetinib) was approved with a REMS that included elements to assure safe use to addresss the risk of QT prolongation, the occurrence of Torsades de pointes and sudden death. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline (Δ QTcF) was 35 ms for Caprelsa. In addition, 36% of patients experienced greater than 60 ms increase in Δ QTcF and 4.3% of patients had QTcF greater than 500 ms. There were 11 cases of sudden death and 2 documented cases of Torsades de pointes (TdP) have occurred with Caprelsa clinical studies.¹⁹

Tasigna (nilotinib) was initially approved with MG and CP in March 2010 and later the REMS is released in May 2013. The maximum mean QTcF change from baseline at steady-state was 10 msec. Increase in QTcF greater than 60 msec from baseline was observed in 4.1% of the patients and QTcF of greater than 500 msec was observed in 4 patients (less than 1%). Ten cases of sudden deaths were reported in the original nilotinib NDA.²⁰ REMS assessments for Tasigna indicated that high percentile of prescriber population are well aware of ECG monitoring intended to identify patients at risk and enhanced early detection and treatment of QT prolongation.²¹

The approved product labels of Caprelsa contain Black Box Warning for QT Prolongation, Torsades De Pointes and Sudden Death whereas Tasigna contain Black Box Warning for QT Prolongation and Sudden Death.^{22,23} Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20 ms at 600 mg once daily dose. In Study A2301, one patient (0.3%) had >500 msec post-baseline QTcF value, and nine patients out of 329 patients (2.7%) had a >60 msec increase from baseline in QTcF intervals. One patient (0.3%) in ribociclib plus letrozole treatment arm, experienced sudden death with Grade 3 hypokalemia and Grade 2 QT prolongation. The patient also known to be on concomitant methadone during treatment with ribociclib though methadone was discontinued three weeks before the sudden death. There were no reported cases of Torsade de Pointes with ribociclib in relation with QT prolongation. The ECG changes occurred within the first 15 days of treatment and were reversible with dose interruption.

Zydelig (idelalisib) was approved with a REMS that consists of a CP to address fatal and/or serious hepatotoxicity. Zydelig's label includes a box warning for the risk of hepatotoxicity and the Warning and Precautions, section 5.1 states, fatal and/or serious hepatotoxicity occurred in 18% of patients treated with Zydelig monotherapy and 11% of patients treated with Zydelig in combination trials. Elevations in ALT or AST greater than 5 times the upper limit of normal have occurred.²⁴ In comparison with the study A2301 for ribociclib, increases in transaminases were observed. Grade 3 or 4 increases in ALT (10% versus 1%) and AST (7% versus 2%) were reported in the KISQALI and placebo arms, respectively. Four patients (1.2%) in the ribociclib plus letrozole group met the biochemical definition of Hy's law; three cases were related to study treatment and none resulted in death.

To better characterize safety the Agency has issued two PMRs and one PMC:^{16,h}

PMR#1:

Conduct a clinical trial to study effect of an alternative dosing regimen (such as 300mg BID or 400mg QD) to the proposed 600mg QD dose. The objective of studying an alternative dosing regimen is to mitigate the risks for QT prolongation without compromising efficacy. The primary safety assessments should include QT prolongation, hepatobiliary toxicities and neutropenia. The primary efficacy endpoint should be objective response rate (ORR).

PMR#2:

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of ribociclib in patients with severe renal impairment.

PMC #1

Submit the overall survival (OS) data and analysis from clinical trial entitled "MONALEESA-2" CLEE011A2301.

DRISK and DOP-1 have determined that if approved, a REMS is not necessary at this time, for ribociclib to ensure the benefits outweigh the risks. Labeling including a Patient Information, routine pharmacovigilance, and post-marketing requirements will be used to communicate the safety issues associated with ribociclib. The adverse events of QT interval prolongation, hepatobiliary toxicity and neutropenia will be included under Warnings and Precautions of the label, and dose modifications to address safety and will be included under section 2, Dosage and Administration. At this time, none of these risks will receive a boxed warning in the label.

A REMS is not necessary to ensure the benefits outweigh the risks of ribociclib for the following reasons: a significant increase in rate of locally assessed PFS was demonstrated favorably with ribociclib plus letrozole arm. Despite the availability of hormone directed therapies for treatment of first-line HR-positive advanced breast cancer, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of advanced breast cancer to extend life,

^h Alebachew, E (E-mail communication to sponsor), dated February 9, 2017

delay disease progression and/or lessen breast cancer related symptoms. The risk of QT interval prolongation, hepatobiliary toxicity and neutropenia and dose modifications to address safety will be communicated in labeling in the Warnings and Precautions section of the label.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable; therefore, if approved, DRISK and DOP-1 concur that a REMS is not necessary for ribociclib to ensure the benefits outweigh the risks. The management of the risks associated with ribociclib treatment can be will be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Mid Cycle Communication, dated January 4, 2017.

11 Appendices

11.1 REFERENCES

¹ Proposed Prescribing Information for Ribociclib as currently edited by the FDA, last updated February 10, 2017.

² Novartis. Clinical Overview for Ribociclib, dated August 29, 2016.

³ <http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics>. Accessed January 6, 2017.

⁴ Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000 Aug 17;406(6797):747-752.

⁵ Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16(1):25-35.

⁶ Taneja P, Maglic D, Kai F, et al. Classical and novel prognostic markers for breast cancer and their clinical significance. *Clin Med Insights Oncol*. 2010;4:15-34.

⁷ Beaver, J & Kordestani, L. Palbociclib Clinical Review, dated January 22, 2015.

⁸ Cardoso, F., et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012; 23 Suppl 7: vii11-19.

⁹ National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed January 9, 2017.

¹⁰ Ibrance. Prescribing Information (last updated 02/2016).

¹¹ Femara. Prescribing Information (last updated 01/2014).

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/s/

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