# Taiwan Food and Drug Administration

# Assessment Report

**Trade Name：擊癌利 200 毫克膜衣錠/KISQAL 200mg Film-Coated Tablets**

**Active Ingredient：ribociclib succinate**

**License Number：MOHW-PI 027320**

**Applicant：台灣諾華股份有限公司**

**Approval Date：107/01/05**

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

## 1. Background Information

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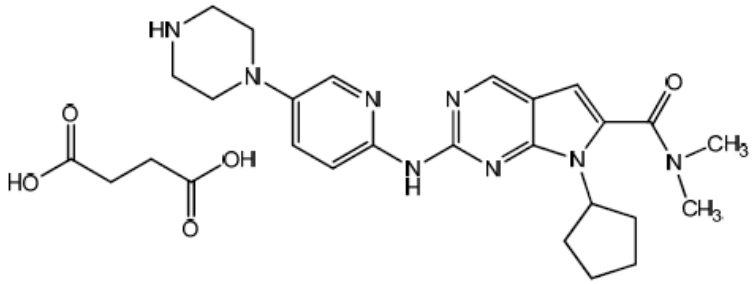
| **Trade Name** | 擊癌利 200 毫克膜衣錠 / KISQALI 200mg Film-Coated Tablets |
| **Active Ingredient(s)** | ribociclib succinate |
| **Applicant** | 台灣諾華股份有限公司 |
| **Dosage Form & Strengths** | 200mg Film-Coated Tablets |
| **Indication** | KISQALI is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)- negative advanced or metastatic breast cancer. |
| **Posology** | The recommended dose is 600 mg (three 200 mg film-coated tablets) of ribociclib taken orally once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days.<br><br>KISQALI should be used together with 2.5 mg letrozole or another aromatase inhibitor. The aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the label of the aromatase inhibitor for additional details.<br><br>Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. |
| **Pharmacological Category ATC Code** | L01XE42 |

## 2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, ribociclib succinate, is chemically designated as 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), and has the following structure:




It is a light yellow to yellowish brown crystalline powder. The molecular formula and the molecular weight are $C_{23}H_{30}N_8O•C_4H_6O_4$ and 552.64 g/mol, respectively. The structure has no chiral center. It is slightly hygroscopic and the solubility is pH-dependent.

Adequate information of characterization of the drug substance has been provided. The structure of ribociclib succinate was confirmed by EA, UV, IR, MS, $^{1}$H-NMR, $^{13}$C-NMR, and X-ray structure analysis. The solid state properties of the drug substance were measured by differential scanning calorimetry, thermogravimetric analysis and X-ray powder diffraction. Production of the correct polymorphic form is ensured by an XRPD method in the active substance specification. The spectrum assignations were consistent with the declared chemical structure.

The specification includes tests for appearance, particle size distribution, clarity of the solution, identification, residual solvents, water content, sulfated ash, metal impurities, related substances, content of ribociclib succinate, assay of succinic acid and microbial enumeration tests.

2.1.2 Drug product

The drug product (KISQALI) is a film-coated tablet containing 200 mg ribociclib as succinate salt packaged in PCTFE/PVC blisters. No novel excipients are used. All excipients used in the drug product formulation are well known pharmaceutical ingredients and their quality is compliant with the compendial monographs. The physicochemical properties of the drug substance, excipient compatibility, and processing considerations guided the selection of the components of the dosage form. A robust process is further confirmed by three consecutive batches of process validation. It has been demonstrated that the manufacturing process is capable of

producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Adequate release and shelf-life specification have been presented for the KISQALI film-coated-tablet and the test items include appearance, identification, mean mass, dissolution, water content, degradation products, microbial enumeration tests and assay. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

## 2.2 Preclinical Pharmacology/Toxicology Evaluation

### 2.2.1 Pharmacological Studies

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 enzyme complex phosphorylates pRb to initiate the G1 to S phase cell cycle transition. In cancers where a functional pRb is present, the CDK4/6 kinase activity is hyper-activated to achieve accelerated cell proliferation. *In vitro* studies demonstrate that ribociclib decreases pRb phosphorylation leading to arrest in G1 phase of the cell cycle and reduced cell proliferation in breast cancer lines. The *in vivo* studies show that ribociclib inhibits tumor growth in a dose-dependent manner in human breast cancer xenograft models. Strong and sustained antitumor effect was observed at combinations of ribociclib with endocrine therapy such as letrozole, fulvestrant and tamoxifen. Rat safety pharmacology studies did not reveal any effects on CNS or respiratory functions. However, ribociclib inhibits hERG potassium channel tail current. *In vivo* cardiac pharmacology safety studies in dogs demonstrate dose and concentration related QTc interval prolongation at an exposure similar to patients receiving the recommended dose of 600 mg. There were no effects on heart rate, blood pressure, core body temperature, or other ECG findings.

### 2.2.2 Toxicological Studies

In the 26-week rat and 39-week dog repeated dose toxicity studies, the hepatobiliary system is the primary target organ of toxicity of ribociclib. Other targets include bone marrow, lymphoid system, testes, epididymis, kidney, intestinal mucosa, skin and bone. The effects on the bone marrow, lymph nodes and thymus, and male reproductive organs are likely related to the primary pharmacological activity of ribociclib. Besides the changes seen in the testes, which showed a trend towards reversibility, other toxicities were reversible. In rats, an increased incidence of

alveolar macrophages in the lung has been noted in all studies. Ribociclib was not considered genotoxic *in vitro* and *in vivo*. Based on the mechanism of ribociclib and the results of reproductive studies in rats (decreased fetal weights with skeletal changes) and rabbits (fetal malformation, visceral and skeletal variations), ribociclib will cause fetal harm when administered to pregnant women.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The active ingredient of KISQALI 200 mg film-coated tablets is ribociclib succinate, which is CDK4/6 inhibitor, and KISQALI is indicated in combination with an aromatase inhibitor 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 peak concentration was achieved rapidly ($T_{max}$ = 1-4 hour) following KISQALI administration. Ribociclib exhibited over-proportional increases in exposure (peak plasma concentration ($C_{max)}$ and area under the time concentration curve (AUC) across the dose range of 50 mg to 1200 mg following both single dose and multiple doses. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and the geometric mean accumulation ratio was 2.51 (range: 0.972 to 6.40). KISQALI can be taken regardless of food because high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib.

*In vitro* human plasma proteins binding of ribociclib was approximately 70% and independent of concentration. *In vivo* blood-to-plasma ratio was approximately 1.04.. The $V_{ss}$/F was 1090 L based on population PK analysis. *In vitro* and *in vivo* studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. 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.

2.3.2 Interaction Studies

Avoid concomitant use of KISQALI with strong CYP3A inhibitors or strong CYP3A4 inducer because the exposure of ribociclib will be influenced. If strong CYP3A4 inhibitors cannot be avoided, reduce KISQALI dose.

2.3.3 Special Populations

No dose adjustment is needed for patients with mild hepatic impairment (Child-Pugh A), However, the recommended starting dose for moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impaired patients is 400 mg Kisqali once daily. Based on the population PK analysis, mild and moderate renal impairment had no

effect on the exposure of ribociclib. The effect of severe renal impairment is still unknown.

Overall, the pharmacokinetic studies met the minimum requirements to support the marketing authorization of KISQALI. It is recommended to approve the NDA of KISQALI from the PK/PD perspective.

## 2.4 Clinical Efficacy and Safety Evaluation

### 2.4.1 Efficacy Results

One multi-center, randomized, double-blind, placebo-controlled Phase III study (CLEE011A2301) was reviewed to evaluate the efficacy of KISQALI (ribociclib) plus letrozole versus placebo plus letrozole in postmenopausal women with HR positive, HER2-negative advanced or metastatic breast cancer who received no prior therapy for advanced disease. Eligible patients were randomized in a 1:1 ratio to either ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily continuous) or placebo (once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily continuous ). Randomization was stratified by the presence of liver and/or lung metastases (yes versus no).

The primary endpoint was progression free survival (PFS) as assessed by the local investigator (RECIST v1.1 criteria). Overall survival (OS) was a key secondary endpoint. The primary analysis of PFS and analyses of OS were performed using a stratified log-rank test. The study planned two PFS analyses, including an interim analysis after approximately 211 (70% information fraction) of the total events and a final analysis after 302 local PFS events, using Haybittle-Peto method. The study also planned a maximum of four analyses for the key secondary endpoint of OS using Lan-DeMets method. The final OS analysis was planned after 400 death events observed.

A total of 668 women (ITT analysis) were randomized (334 patients to the ribociclib plus letrozole arm and 334 patients to the placebo plus letrozole).

The interim analysis of investigator-assessed PFS was performed when 243 total progressions occurred (80.5% of the planned events for the final PFS analysis). The investigator-assessed PFS was significant longer in the ribociclib plus letrozole arm, where the median was not reached (95% CI: 19.3-NE) versus 14.7 months (95% CI: 13.0-16.5) in the placebo plus letrozole arm (hazard ratio 0.556; 95% CI: 0.429-0.720; stratified log-rank test $p=3.29*10^{-6}$). The PFS assessment based on a blinded independent central radiological (BICR) review was consistent with

investigator assessment.

The key secondary endpoint of OS was first tested with a total of 43 deaths (10.8% of the planned events for the final OS analysis) at the time of the interim analysis for PFS, and was also tested at a 2nd interim analysis (19.3% of the planned events for the final OS analysis); neither of them exceed the corresponding stopping boundary.

Objective response rate (ORR) was 52.7% (95% CI: 46.6, 58.9) in the ribociclib plus letrozole arm and 37.1% (95% CI: 31.1, 43.2) in the placebo plus letrozole arm.

A clinically relevant effect in PFS has been demonstrated for the combination therapy of ribociclib with letrozole for the treatment of postmenopausal women with HR positive, HER2 negative advanced or metastatic breast cancer as initial endocrine based therapy. Supportive ORR, BICR, and subgroup analyses further substantiate the evidence of ribociclib benefit. Despite the OS findings are still immature, a reassuring trend towards benefit for the ribociclib arm has been observed. Overall, the efficacy is acceptable.

### 2.4.2 Safety Results

The safety data are based on CLEE011A2301, a clinical study of 668 postmenopausal women receiving KISQALI(ribociclib) plus letrozole or placebo plus letrozole. The median duration of exposure to ribociclib plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving ribociclib plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving ribociclib plus letrozole and 2% in patients receiving placebo plus letrozole. The most common ARs leading to treatment discontinuation of ribociclib in patients receiving ribociclib plus letrozole were ALT increased (4%), AST increased (3%), vomiting (2%).

On-treatment deaths, regardless of causality, were reported in three cases (0.9%) of ribociclib plus letrozole treated patients vs. one case (0.3%) of placebo plus letrozole treated patients. Causes of death on ribociclib plus letrozole included one case each of the following: progressive disease, death (cause unknown), and

sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation). The most common ARs (reported at a frequency ≥ 20%) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain. The most common Grade 3/4 ARs (reported at a frequency > 2%) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

QT interval was prolonged in a concentration dependent manner in patients treated with ribociclib. One patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the ribociclib plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm.

The combination of ribociclib to letrozole is associated with an increase in toxicity relative to letrozole alone. Neutropenia appeared to be appropriately managed as evidenced a low frequency of discontinuations. Hepatobiliary toxicity was manageable with appropriate dose modifications which are clearly delineated in labeling. Risk of QT prolongation has been addressed by label as warnings and precautions and dose modifications are clearly delineated. A postmarketing requirement (3168-1) required by US FDA will be conducted to study an alternative dosing regimen in order to mitigate the risks for QT prolongation without compromising efficacy. The applicant is required to submit the result of the above study to TFDA after it is available. In conclusion, the safety of ribociclib appears acceptable and manageable for the intended population.

## 2.5 Bridging Study Evaluation

The exposure of Japanese was higher than that of Caucasian with difference of CL/F and $T_{1/2.}$ However, from Study CLEE011A2115C, the exposure of Singapore/Hong Kong patients was similar to that of Caucasian. It remained to be determined that why the exposure was different between Japanese and Asian non-Japanese.

Study CLEE011A2115C was a phase Ib dose escalation study of the combination of ribociclib with letrozole and dose expansion of ribociclib with hormonal

therapy for the treatment of pre-(with goserelin) and postmenopausal women with HR positive, HER2-negative, advanced breast cancer. The purpose of the phase Ib was to determine the recommended dose of ribociclib in combination with letrozole in Asian non-Japanese patients and Japanese patients. The results of Japanese patients in CLEE011A2115C were not available during BSE review. According to the preliminary report provided by the applicant, based on 26 Asian non-Japanese patients from predominantly Hong Kong and Singapore, the recommended phase 2 dose was determined to be 600mg once daily, 3 weeks on, 1 week off in combination with letrozole. This dose was the same as that used in the Caucasian population.

In Study CLEE011A2301, a total of 41 East Asian (6.1% of total population) were enrolled. Based on limited East Asian data, the efficacy was similar between East Asian and Non-East Asian, the incidences of neutropenia and thrombocytopenia were numerically higher in East Asian compared to Non-East Asian.

In Study CLEE011A2115C, the 26 Asian non-Japanese patients were considered ethnically similar to Taiwanese. The exposure of Asian non-Japanese was similar to that of Caucasian. The recommended phase 2b dose of Asian non-Japanese was similar to that of Caucasian. Based on limited East Asian data from CLEE011A2301(22 patients received ribociclib, 19 patients received placebo), it was inconclusive whether the incidences of neutropenia and thrombocytopenia were different between East Asian and Non-East Asian. However, even if difference did exist, these adverse events are clinically manageable with close monitor and dose modification. In conclusion, ribociclib was not considered ethical sensitive and bridging study was waived.

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2.6 Conclusion

The benefit risk ratio is considered positive for the intended population. Ribociclib is approved for the following indication:
“KISQALI is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer”

## 3. Post-Marketing Requirements

The applicant is required to submit the final results of Study CLEE011A2301 and the postmarketing requirement 3168-1 (required by US FDA). Routine

pharmacovigilance is also required.