CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212436Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 31, 2019
From	Pengfei Song
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA/BLA # and Supplement#	NDA 212436; Associated with NDA 207103
Applicant	Pfizer, Inc
Date of Submission	January 31, 2019
PDUFA Goal Date	October 31, 2019
Proprietary Name	IBRANCE®
Established or Proper Name	Palbociclib
Dosage Form(s)	Tablets: 125 mg, 100 mg, and 75 mg.
Indication(s)/Population(s)	IBRANCE is indicated for the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: • an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or • fulvestrant in women with disease progression following endocrine therapy.
Dosing Regimen(s)	125 mg once daily taken orally with or without food for 21 days followed by 7 days off treatment.
Recommendation on Regulatory Action	Approval

1. Background

IBRANCE (Palbociclib) was approved in 2015 with a capsule formulation under NDA207103. IBRANCE capsule is indicated for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. The recommended starting dose of IBRANCE capsule is 125 mg once daily taken with food for 21 days followed by 7 days off treatment. The capsule should be administered with food to reduce variability in drug absorption and to mitigate drug-drug-interactions (DDIs) with gastric acid reducing agents.

In the current submission, the applicant seeks the full approval of newly developed IBRANCE tablet formulation for oral use in the currently marketed indications of the capsule formulation. Ibrance tablets are formulated as immediate release film-coated tablet supplied in 75 mg, 100 mg, and 125 mg strength, same strength as the currently approved capsules. The tablets are packaged in (b) (4) blisters (b) (4) The proposed dosing regimen of the commercial tablets is same with the commercial capsule formulation: 125 mg once daily taken orally with or without food for 21 days followed by 7 days off treatment.

The Applicant submits pharmacokinetic (PK) evidence from clinical studies in healthy volunteers to support the approval of the proposed tablet formulation.

2. Summary of Disciplinary Reviews

The following is a summary of disciplinary reviews documented in DARRTs:

2.1. CMC

The product quality review team (consisting of the following disciplines: API, drug product, manufacturing process/facility and biopharmaceutics) recommends Approval of this NDA. Complete CMC information has been submitted to NDA 212436 and found to be adequate upon completion of the review. No PAI (pre-approval inspection) was conducted for the NDA as all API and drug product facilities are found adequate upon review of the inspection history.

Drug Substance

The drug substance, palbociclib, is a (b) (4) which is also the form used in the commercial Ibrance capsules (NDA 207103). There is no drug substance information needs to be reviewed since it is referenced to the applicant's approved NDA 207103.

Drug Product

The drug product information is found acceptable.

The applicant provided satisfactory drug product information including adequate stability data for Ibrance (palbociclib) tablet. The proposed Ibrance film-coated tablets for oral administration are supplied as 75 mg, 100 mg, and 125 mg in (b) (4) blisters (1 tablet per cell, 7 tablets in each blister pack and 21 tablets in each monthly box). Pfizer is not planning to (b) (4) (b) (4) (b) (4) formulated as immediate release, film coated tablets containing palbociclib and common pharmaceutical excipients. Unlike Ibrance capsule that should be taken with food, (b) (4)

(b) (4)

Manufacturing

The status of all drug substance and drug product manufacturing and testing facilities is found CGMP compliant. No PAI is needed. The overall DP manufacturing process and facility information is deemed acceptable.

The manufacturing process of the drug product includes (b) (4)

(b) (4)

Biopharmaceutics

The biopharmaceutical information is deemed acceptable.

The Biopharmaceutics review is focused on the evaluation of the 1) proposed in vitro dissolution method and acceptance criterion, and (2) formulation bridging. Palbociclib has poor aqueous solubility in the physiological pH range (high solubility at low pH), and low permeability. The proposed QC dissolution method (USP Apparatus 2 at 75 rpm) is discriminating for (b) (4)

(b) (4)

(b) (4)

Bridging of the clinical to the To-Be-Marketed drug product has been demonstrated. The proposed commercial tablet (125 mg) is the same formulation as the tablet evaluated in the Pivotal BE Study, and is manufactured using the same drug product manufacturing process. Additionally, the proposed commercial tablets will be manufactured at a similar batch size as the lots used in registration stability and the pivotal BE studies.

The Applicant's request to waive the requirement to conduct an in vivo BA or BE study for the two lower strengths (75 mg and 100 mg) of the proposed commercial tablet is granted based on the evidence of (b) (4) and comparable in vitro dissolution profile data of the test and reference strengths, using the proposed QC dissolution method that was shown to be clinically relevant. Additionally, the Applicant noted that palbociclib PK are dose proportional across the (b) (4) dose range.

Environmental Assessment

It is acceptable. The applicant requested categorical exclusion from the requirement for environmental impact assessment per 21 CFR 25.31. Based on their knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment based on 21 CFR 25.15(d). In addition, the proposed tablet formulation is to replace the currently marketed capsule formulation. There is no increased usage/production expected.

2.2. Clinical Pharmacology

The Office of Clinical Pharmacology concluded that the proposed tablet formulation allows for administration of palbociclib with or without food and concomitant administration of proton pump inhibitors (PPIs) under any food intake condition. The applicant provided adequate pharmacokinetic (PK) evidence from clinical studies in health volunteers to support the proposed tablet formulation. Specifically, the Applicant provided the following evidence:

1. Study A5481081 provided PK evidences to establish the bioequivalence (BE) between the current commercial capsules and the proposed commercial tablets, as well as between the tablets taken with or without food.

   Study A5481081 was a Phase 1, open-label, randomized, single-dose, 4-period, 4-sequence crossover study in healthy volunteers (Table 1). This study consisted of 4 treatments of palbociclib with two different formulations:
   - Treatment A (reference): 125 mg capsule given with a moderate-fat/standard-calorie meal (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively)
   - Treatment B (Test): 125 mg tablet given with a moderate-fat/standard-calorie meal
   - Treatment C (Test): 125 mg tablet given under fasting conditions (following an overnight fast of at least 10 hours)

- Treatment D (Test): 125 mg tablet given with a high-fat/high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively)

The results established the bioequivalence, as shown in the table below:

Table 1. Palbociclib PK Parameters to Establish BE Between the Commercial 125 mg Capsule and the Proposed Commercial 125 mg Tablet of Palbociclib

Parameter (units)	Adjusted Geometric Means Test	Adjusted Geometric Means Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Tablet Fasted (Test) vs. Capsule Moderate-fat Fed (Reference)				
AUC_{inf} (ng•hr/mL)	1414	1550	91.22	(88.69, 93.82)
AUC_{last} (ng•hr/mL)	1365	1501	90.91	(88.32, 93.58)
C_{max} (ng/mL)	46.11	50.62	91.09	(87.21, 95.15)
Tablet Moderate-fat Fed (Test) vs. Capsule Moderate-fat Fed (Reference)				
AUC_{inf} (ng•hr/mL)	1537	1550	99.18	(96.41, 102.03)
AUC_{last} (ng•hr/mL)	1489	1501	99.21	(96.36, 102.14)
C_{max} (ng/mL)	50.73	50.62	100.22	(95.91, 104.71)
Tablet High-fat Fed (Test) vs. Capsule Moderate-fat Fed (Reference)				
AUC_{inf} (ng•hr/mL)	1721	1550	111.01	(107.91, 114.19)
AUC_{last} (ng•hr/mL)	1673	1501	111.45	(108.24, 114.74)
C_{max} (ng/mL)	58.31	50.62	115.19	(110.25, 120.36)

a. The ratios (and 90% CIs) are expressed as percentages.

Source: Table 10 of Full Clinical Study Report Protocol A5481081

2. Study A5481081 provided the PK evidence that there is no clinically significant food effect for the proposed commercial tablet formulation: The ratios of adjusted geometric means (Fed/Fasted) for AUCinf and Cmax were 121.69% (90% CI: 118.30%, 125.19%) and 126.46% (90% CI: 121.03%, 132.13%), respectively.

3. Study A5481091 provided the PK evidence that there are no clinically relevant drug-drug interactions between the proposed commercial tablets and proton pump inhibitors (PPIs): PK profiles were similar between the proposed commercial tablet with or without concomitant use of rabeprazole.

   The Study was a Phase 1, open-label, 2-period, fixed sequence study to investigate the effect of multiple doses of a PPI (rabeprazole) on palbociclib PKs in healthy subjects. 12 subjects received Treatment A first and then Treatment B with a washout period of at least 10 days between the 2 single doses of palbociclib (Figure 2).

   - Treatment A (Reference): a single oral dose of the 125 mg tablet given under fasted conditions (following an overnight fast of at least 10 hours)
   - Treatment B (Test): 2 x 20 mg oral rabeprazole tablets QD given in the morning from Day -6 to Day -1 at approximately 30 minutes before food intake. On Day 1, the single oral dose of the 125 mg commercial tablet was given under fasted conditions (10 hours fasting) at least 4 hours after the administration of 2 x 20 mg dose of rabeprazole under fasted conditions).

Table 2. Statistical Comparison of Palbociclib PK Parameters Between Palbociclib Alone (Reference) and Palbociclib with Rabeprazole (Test)

Pharmacokinetic Parameter (Unit)	Adjusted Geometric Means Rabeprazole + Palbociclib (Test)	Palbociclib Alone (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio[a]
AUC_{inf} (ng·hr/mL)	1408.32	1322.79	106.47	(99.22, 114.24)
AUC_{last} (ng·hr/mL)	1360.95	1278.91	106.42	(99.11, 114.25)
C_{max} (ng/mL)	44.82	45.99	97.45	(90.44, 104.99)

a. The ratios (and 90% CIs) are expressed as percentages.

Source: Table 14.4.5.3.1 of Full Clinical Study Report Protocol A5481091

2.3. Clinical

No changes were made to the efficacy or safety sections of the USPI. The application references the original safety and efficacy data from NDA 207103. The tablet formulation has been only tested as single-dose administrations in healthy volunteers in 4 studies. There were no deaths, SAEs, or new unexpected TEAEs from these studies.

2.4. Nonclinical

Nonclinical Pharmacology/Toxicology review recommend approval, with no need for additional nonclinical study or labeling changes. For the proposed tablet formulation of palbociclib, the CMC review team requested an assessment of 3 impurities in the drug product with specified limits above ICH Q3A/B limits. The Applicant's proposed specification limits for (b) (4), (b) (4) and (b) (4) at (b) (4)%, (b) (4)% and (b) (4)%, respectively, are acceptable as they are metabolites in human and animals, and (b) (4) was also controlled at (b) (4)% in the commercial IBRANCE capsules.

3. Labeling

The proposed Ibrance PI received on January 31, 2019 is generally acceptable, and the FDA's recommendations in the labeling language have been agreed by the Applicant.

4. Recommendations/Risk Benefit Assessment

Based on the disciplinary reviews, the CDTL reviewer concludes that the proposed Ibrance tablet formulation is approvable. The new tablet formulation allows for administration of palbociclib with or without food and concomitant administration of PPIs under any food intake condition. The applicant has provided adequate evidence to support the proposed tablet formulation for approval.

Recommended Comments to Applicant

FDA has the following recommendation on the proposed container label and carton labeling for the blister packs for further improvement to ensure safe product use. The recommendation should be implemented at the next printing:

1. Revise the strength statement that immediately follows the established name to “XX mg per tablet” or “XX mg/tablet” so that the strength statement clearly indicate that XX mg is in each tablet and to prevent the risk of medication error associated with confusion that XX mg is the total contents of the entire blister pack. We acknowledge that Ibrance capsules container labels use “XX mg” instead of “XX mg per tablet”. However, because the proposed Ibrance tablets are packaged in a blister containing 7 tablets, there is risk that patients may think they need to take all 7 tablets to achieve the “XX mg” strength. This risk is unique to the proposed blister pack container closure. See draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Recommended Regulatory Action

Approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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