CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212436Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	212436
Link to EDR	\\cdsesub1\evsprod\nda212436\0001\
Submission Date	1/31/2019
Submission Type	NDA
Brand Name	IBRANCE
Generic Name	Palbociclib
Dosage Form and Strength	Tablets: 125 mg, 100 mg, and 75 mg.
Route of Administration	125 mg once daily taken orally with or without food for 21 days followed by 7 days off treatment.
Proposed Indication	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.
Applicant	Pfizer
Associated NDA	NDA-207103
OCP Review Team	Wentao Fu, Ph.D.; Pengfei Song, Ph.D.

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1. EXECUTIVE SUMMARY

IBRANCE (palbociclib) was approved in 2015 with a capsule formulation under NDA 207103. 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 a newly developed IBRANCE tablet formulation for oral use in the currently marketed indications of the capsule formulation. The proposed dosing regimen of the commercial tablets is 125 mg once daily taken orally with or without food for 21 days followed by 7 days off treatment. The proposed commercial tablets and the commercial capsules have the same starting dose (125 mg) and strengths (125 mg, 100 mg, and 75 mg).

The proposed tablet formulation allows administration of palbociclib with or without food and concomitant administration of 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.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 212436 submission. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Evidence of PK bioequivalence (BE) between the commercial capsules and the proposed commercial tablets.	A Phase 1 trial (Study A5481081) demonstrated PK BE between the commercial capsules and the proposed commercial tablets.
Evidence of the proposed commercial tablets can be taken with or without food.	A Phase 1 trial (Study A5481081) demonstrated no clinically significant food effect for the proposed commercial tablets.
Evidence of no DDIs between the proposed commercial tablets and proton pump inhibitors (PPIs).	A Phase 1 trial (Study A5481091) demonstrated no DDIs between the proposed commercial tablet formulation and rabeprazole (a PPI).

1.2 Post-Marketing Requirements and Commitments

None.

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2. CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacokinetics

2.1.1 Study A5481081: PK BE evaluation between the commercial capsules and the proposed commercial tablets.

Study A5481081 provided evidences of PK 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)

Table 1. Study A5481081 Design

Sequence Group	Period 1		Period 2		Period 3		Period 4
Sequence 1	A		B		C		D
Sequence 2	B	Washout	C	Washout	D	Washout	A
Sequence 3	C		D		A		B
Sequence 4	D		A		B		C

Source: Table 1 of Full Clinical Study Report Protocol A5481081.

A total of 44 subjects (11 per sequence) were enrolled in the study. Each subject received one of the 4 treatments in each period with at least 10 days for washout. In each period, subjects underwent serial blood sampling for PK at predose, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours following palbociclib administration. Two subjects discontinued from the study due to family reasons. Subject (b) (6) received all 4 study treatments and discontinued during Period 4 (Treatment B). Subject (b) (6) did not receive the fourth study treatment (scheduled to be Treatment D).

The to-be-marketed commercial tablet contains 3 dose strengths of 75 mg, 100 mg, and 125 mg. These 3 tablet strengths have the same qualitative composition, are quantitatively proportional formulations, and are produced following the same manufacturing processes. There are no clinical study results for the proposed 100 mg and 75 mg tablets in this submission. To support the performance equivalence of the different tablet strength formulations, an in vitro approach (a dissolution similarity assessment of the 3 tablet strengths) was performed according to the

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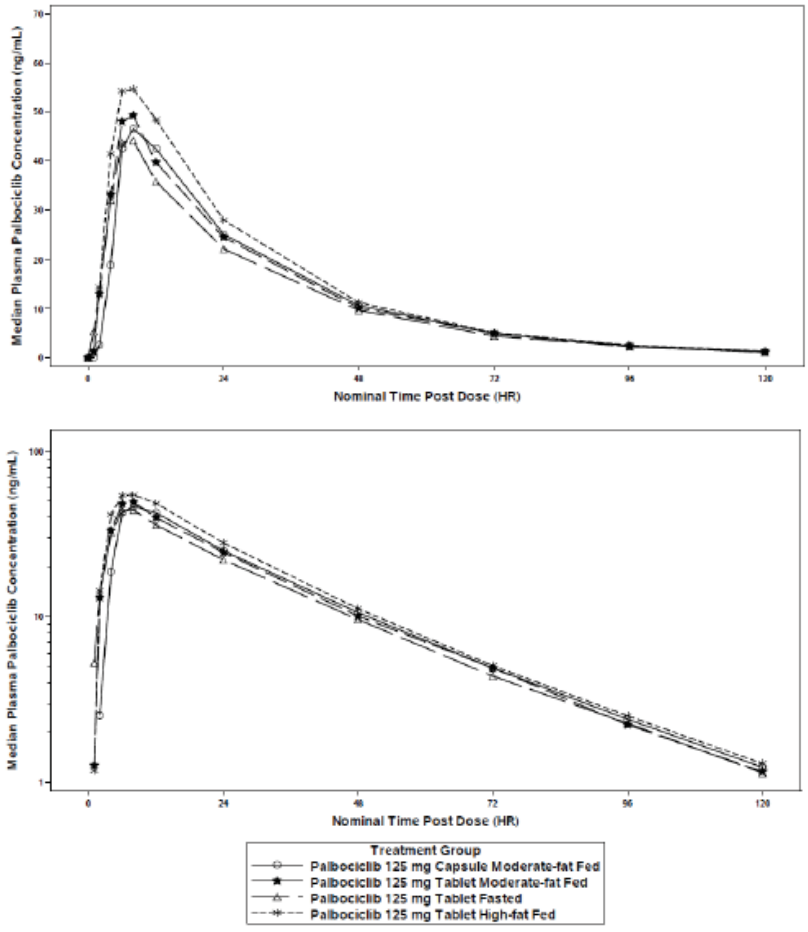
CHMP Guideline on the Investigation of Bioequivalence. Please refer to the Biopharmaceutics review on the in vitro assessment.

Following a single-dose of palbociclib, PK profiles were similar between the proposed commercial tablet (under overnight fasting conditions, with a moderate-fat/standard-calorie meal and with a high-fat/high-calorie meal) and the commercial capsule formation (with a moderate-fat/standard-calorie meal) (Figure 1). The PK parameters from the tablet regardless of meal (under overnight fasting conditions, with a moderate-fat/standard-calorie meal and with a high-fat/high-calorie meal) and the commercial capsule formation with a moderate-fat/standard-calorie meal are similar, Table 2. The statistical analysis $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} of palbociclib meet BE criteria, Table 3.

Of note, the commercial capsules under fasted conditions, lower palbociclib exposure was found to occur in 13% of patients' PK profiles (defined as "low-liers" subpopulation by the applicant). Food intake eliminated the occurrence of "low-liers" and reduced the inter- and intra-subject variability in palbociclib exposure for the commercial capsules (See the clinpharm review for the original palbociclib NME NDA 207103 in DARRTs dated 1/15/2015 for details).

Figure 1. Median Plasma Palbociclib Concentration-Time Profiles Following Single Oral 125 mg Dose of Palbociclib



Upper and lower panels are linear and semi-logarithmic scales, respectively.

Source: Figure 1 of Full Clinical Study Report Protocol A5481081

Table 2. Summary of Plasma PK Parameters

Parameter Summary Statistics[a] by Treatment				
Parameter (units)	Capsule Moderate-fat Fed	Tablet Moderate-fat Fed	Tablet Fasted	Tablet High-fat Fed
N, n	44, 44	43, 43	44, 44	43, 43
AUC_{inf} (ng•hr/mL)	1550 (25)	1534 (25)	1414 (26)	1724 (23)
AUC_{last} (ng•hr/mL)	1501 (26)	1486 (25)	1365 (27)	1676 (23)
C_{max} (ng/mL)	50.62 (27)	50.39 (26)	46.11 (31)	58.47 (27)
T_{max} (hr)	8.00 (6.00-12.0)	6.02 (4.00-12.1)	6.00 (4.00-8.10)	6.00 (4.00-12.5)
$t_{½}$ (hr)	22.38 ± 3.19	22.34 ± 2.90	22.55 ± 3.17	22.18 ± 2.91
CL/F (L/hr)	80.67 (25)	81.49 (25)	88.41 (26)	72.53 (23)
V_z/F (L)	2578 (26)	2604 (25)	2847 (27)	2301 (23)

[a]. *Geometric mean (geometric %CV) for all except: median (range) for Tmax; arithmetic mean (±SD) for t½.*

Source: Table 9 of Full Clinical Study Report Protocol A5481081

Table 3. Statistical Summary of Palbociclib PK Parameters to Establish BE Between the Commercial 125 mg Capsule and the Proposed Commercial 125 mg Tablet of Palbociclib

	Adjusted Geometric Means		Ratio	90% CI
Parameter (units)	Test	Reference	(Test/Reference) of Adjusted Means[a]	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

2.1.2 Study A5481081: The food effect of the proposed commercial tablets

The statistical comparisons of palbociclib PK parameters to evaluate the relative bioavailability for the proposed commercial tablet following administration under fasted or fed (moderate-fat or a high-fat meal) conditions are summarized in Table 4. The ratios of adjusted geometric means (Test/Reference) for AUC_{inf} and C_{max} were 121.69% (90% CI: 118.30%, 125.19%) and 126.46% (90% CI: 121.03%, 132.13%), respectively. The results suggested that there is no clinically significant food effect for the proposed commercial tablet.

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Table 4. Statistical Summary of Palbociclib PK Parameters of the 125-mg Commercial Tablet Under Different Fasted and Fed Conditions

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Tablet Fasted (Test) vs. Tablet Moderate-fat Fed (Reference)				
AUC_{inf} (ng•hr/mL)	1414	1537	91.97	(89.40, 94.61)
AUC_{last} (ng•hr/mL)	1365	1489	91.64	(89.00, 94.35)
C_{max} (ng/mL)	46.11	50.73	90.90	(87.00, 94.98)
Tablet High-fat Fed (Test) vs. Tablet Moderate-fat Fed (Reference)				
AUC_{inf} (ng•hr/mL)	1721	1537	111.92	(108.77, 115.16)
AUC_{last} (ng•hr/mL)	1673	1489	112.33	(109.08, 115.68)
C_{max} (ng/mL)	58.31	50.73	114.95	(109.98, 120.14)
Tablet High-fat Fed (Test) vs. Tablet Fasted (Reference)				
AUC_{inf} (ng•hr/mL)	1721	1414	121.69	(118.30, 125.19)
AUC_{last} (ng•hr/mL)	1673	1365	122.59	(119.07, 126.22)
C_{max} (ng/mL)	58.31	46.11	126.46	(121.03, 132.13)

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

Source: Table 11 of Full Clinical Study Report Protocol A5481081

2.1.3 Study A5481091: DDIs between the proposed commercial tablets and proton pump inhibitors (PPIs)

Study A5481091 provided evidences of no DDIs between the proposed commercial tablets and PPIs. 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)

Blood samples for PK analysis of palbociclib were taken at pre-dose (within approximately 1 hour prior to palbociclib dosing), 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours post-dose.

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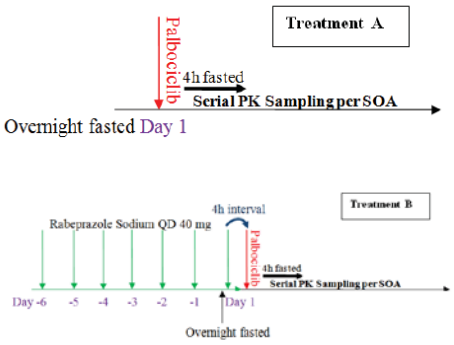
Figure 2. Study A5481091 Study Design



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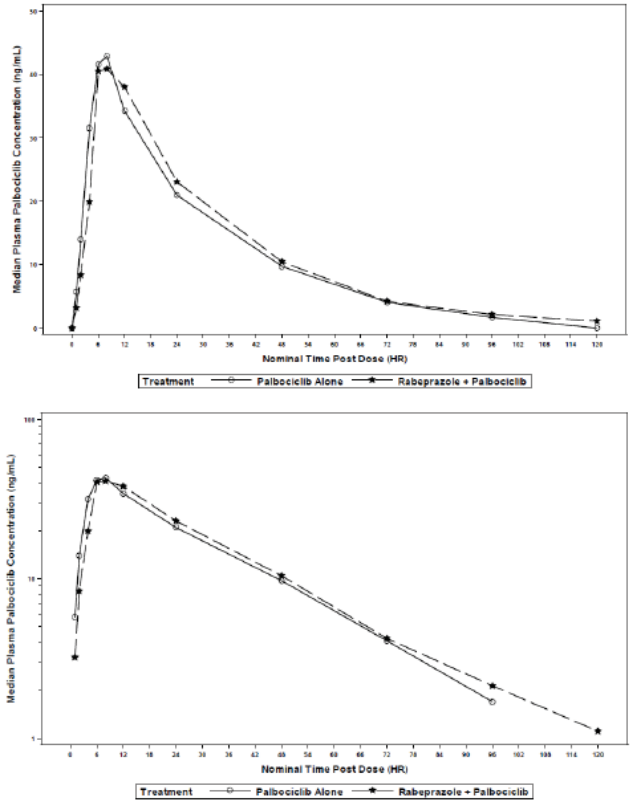
Source: Figure 1 and 2 of Full Clinical Study Report Protocol A5481091

Following a single-dose of palbociclib under overnight fasting conditions, PK profiles were similar between the proposed commercial tablet with or without concomitant use of rabeprazole, Figure 3 and Table 5. The statistical analysis of AUC_{inf}, AUC_{last} and C_{max} were within the BE criteria.

Figure 3. Study A5481091 Palbociclib Plasma Concentration-Time Profiles Following Administration of Palbociclib Single Oral Dose (125 mg) Alone or in Combination With Multiple Oral Doses of Rabeprazole (40 mg QD)



upper and lower panels are linear and semi-logarithmic sca

Source: Figure 14.4.4.2.1.1 and 14.4.4.2.1.2 of Full Clinical Study Report Protocol A5481091

Table 5. Study A5481091 Palbociclib PK Parameters

Pharmacokinetic Parameter (Unit)	Summary Statistics[a] by Treatment	
	Palbociclib Alone	Rabeprazole + Palbociclib
N, n	12, 12	12, 12
AUC_{inf} (ng·hr/mL)	1323 (21)	1408 (21)
AUC_{last} (ng·hr/mL)	1279 (21)	1361 (21)
C_{max} (ng/mL)	45.99 (27)	44.82 (26)
T_{max} (hr)	6.02 (6.00-12.0)	8.00 (6.00-12.0)
$t_{½}$ (hr)	19.93 ± 2.97	22.36 ± 3.68
CL/F (L/hr)	94.50 (21)	88.69 (21)
V_z/F (L)	2694 (24)	2827 (23)

Source: Table 14.4.5.1.1 of Full Clinical Study Report Protocol A5481091

Table 6. Statistical Comparison of Palbociclib PK Parameters Between Palbociclib Alone (Reference) and Palbociclib with Rabeprazole (Test)

Pharmacokinetic Parameter (Unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio[a]
	Rabeprazole + Palbociclib (Test)	Palbociclib Alone (Reference)		
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

2.2 General Dosing

The recommended starting dosage for the proposed commercial tablets is 125 mg once daily taken orally with or without food for 21 days followed by 7 days off treatment. The dose is the same as the recommended starting dose of the commercial capsules, except for food consumption conditions. The proposed commercial tablets dosage is supported by the BE between the commercial capsules and the proposed commercial tablets as well as the no clinically significant food effect for the proposed commercial tablet.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The applicant proposed labeling changes are in the left column. FDA proposed labeling changes are in the right column. The changes of red fonts proposed by the applicant to black ones with underscore indicate the content is acceptable. FDA proposed labeling changes were conveyed to the applicant on August, 2019. The applicant agreed with all the changes. There are multiple changes of tablets to capsules and food consumption conditions in the labeling. The following

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table only highlight the changes made under Dosage and Administration. Please refer to the labeling for all other changes.

The Applicant's Proposed Labeling Changes	FDA Proposed Labeling Changes
---------- DOSAGE AND ADMINISTRATION ---------- (b) (4)	**---------- DOSAGE AND ADMINISTRATION ----------** IBRANCE tablets are taken orally with or without food in combination with an aromatase inhibitor or fulvestrant. (2) Recommended starting dose: 125 mg once daily taken with or without food for 21 days followed by 7 days off treatment. (2.1)
12.3 Pharmacokinetics …… **Absorption** The (b) (4) maximum observed concentration (Cmax) of palbociclib is generally observed (b) (4) between (b) (4) to 12 hours (time to reach maximum concentration, T_{max}) following oral administration of IBRANCE tablets. Food Eeffect: The area under the concentration-time curve from zero to infinity (AUC_{INF}) and C_{max} of palbociclib increased by 22% and 26%, respectively, when IBRANCE tablets were 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), and by 9% and 10%, respectively, when IBRANCE tablets were 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), compared to IBRANCE tablets given under overnight fasted conditions.(b) (4) (b) (4)	**12.3 Pharmacokinetics** …… **Absorption** The maximum observed concentration (Cmax) of palbociclib is generally observed between 4 to 12 hours (time to reach maximum concentration, T_{max}) following oral administration of IBRANCE tablets. Food Effect: The area under the concentration-time curve from zero to infinity (AUC_{INF}) and C_{max} of palbociclib increased by 22% and 26%, respectively, when IBRANCE tablets were 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), and by 9% and 10%, respectively, when IBRANCE tablets were 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), compared to IBRANCE tablets given under overnight fasted conditions …… *Gastric pH Elevating Medications* In a drug interaction trial in healthy subjects, coadministration of a single 125 mg IBRANCE tablet with multiple doses of the proton pump inhibitor (PPI) rabeprazole under overnight fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg IBRANCE tablet administered alone. Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, an effect of these classes of acid reducing agents on palbociclib exposure is not expected.

(b) (4)	

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