CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212436Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212436
Supporting document/s:	0001
Applicant's letter date:	January 31, 2019
CDER stamp date:	January 31, 2019
Product:	IBRANCE (palbociclib)
Indication:	women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer
Applicant:	Pfizer Inc.
Review Division:	Division of Hematology Oncology Toxicology
	(for Division of Oncology Products 1)
Reviewer:	Wei Chen, PhD
Supervisor/Team Leader:	Tiffany Ricks, PhD (acting)
Division Director:	John Leighton, PhD, DABT
	(Julia Beaver, MD)
Project Manager:	Kim Robertson

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1 Executive Summary

1.1 Introduction

IBRANCE (palbociclib) is a first in class small molecule inhibitor of cyclin dependent kinases (CDK) 4 and 6. Capsule formulation for IBRANCE was approved in the United States (US) under NDA 207103 for currently marketed indications. The Applicant submitted this NDA to seek full approval for IBRANCE® (palbociclib) proposed tablet formulation for oral use in the currently marketed indications.

1.2 Brief Discussion of Nonclinical Findings

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 proposed specification limits for [redacted] and [redacted] at [redacted]%, [redacted]% and [redacted]%, respectively.

The proposed specification limits of [redacted] and [redacted] at [redacted]% and [redacted]%, respectively, are acceptable as they are metabolites in human and animals, and [redacted] was also controlled at [redacted]% in the commercial IBRANCE capsules.

To qualify impurity [redacted], the Applicant conducted a GLP compliant 1-month repeat-dose rat toxicology study with palbociclib containing [redacted] and submitted results in this application. Based on no-observed-adverse-effect levels (NOAEL) of 10 mg/kg/day in males and 200 mg/kg/day in females identified in a 15-week oral dose study of palbociclib (Study #12LJ025), the same dose levels were selected for male and female rats. [redacted] was spiked into a batch of palbociclib at a level of [redacted]% [redacted] human equivalent dose [HED]) for males and [redacted]% [redacted] HED) for females. The administration of palbociclib in the presence of impurity [redacted] resulted in test article-related changes including limited to mild alterations in some hematology test parameters, decreased organ weight parameters (prostate, thymus, and spleen), and a microscopic finding of minimal hypocellular sternum marrow. The addition of [redacted] did not change the toxicity profile and TK parameters of palbociclib. The Applicant also assessed the structure of [redacted] using two complementary (Q)SAR methodologies including DEREK, and no mutagenicity alert for [redacted] was identified. At the proposed specified level o [redacted]%, patients would receive [redacted] impurity [redacted] at the recommended dose of 125 mg/day palbociclib. Based on the nonclinical data submitted, the proposed specification limit of [redacted]% [redacted] is acceptable from a pharmacology/toxicology perspective.

The potential risk of palbociclib to fetal development based on the mechanism of action of the drug was included in the IBRANCE label. Prenatal and postnatal developmental toxicity studies are not warranted for the approved indication. The Applicant conducted a prenatal and postnatal developmental toxicity study in rats with palbociclib and submitted results in this application. The study showed that there were palbociclib-related adverse lower mean maternal (F0) body weight gain during the gestation dosing phase [redacted]x control for the interval of GD 6 to 20), which resulted in lower mean maternal (F0) body weights on GD 20 ([redacted]x control) at 300 mg/kg/day.

There were also palbociclib-related adverse lower mean maternal (F0) food consumption at 300 mg/kg/day during the gestation dosing phase (0.89x control for the interval of GD 6 to 21). There were no adverse effects on the F1 generation. The Applicant did not request to update the label with the findings from the conducted prenatal and postnatal development study results. The IBRANCE label currently includes a Warning and Precaution for embryo-fetal toxicity and supporting animal data. Administration of palbociclib to pregnant rats and rabbits during the period of organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposures based on AUC. The lack of findings in the prenatal and postnatal development study in rats under the conditions tested did not exclude the potential risk of palbociclib on fetal development.

1.3 Recommendations

1.3.1 Approvability

Recommending approval.

1.3.2 Additional Non Clinical Recommendations

Additional nonclinical studies are not needed at this time.

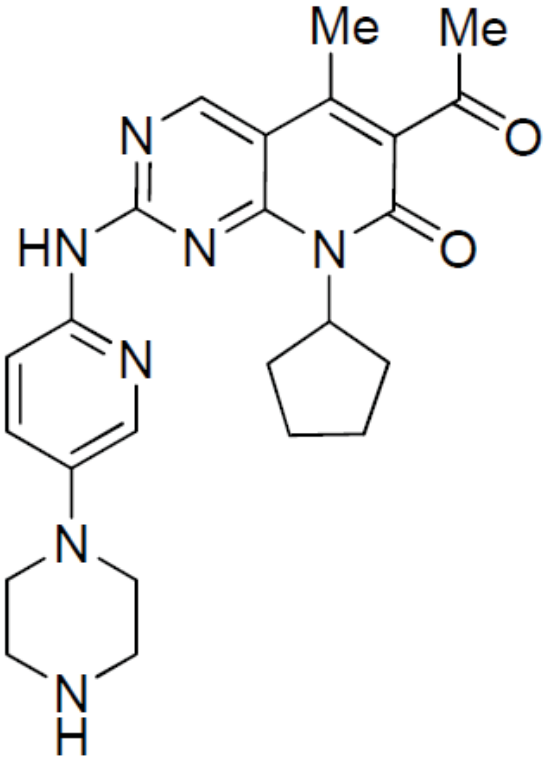
1.3.3 Labeling

No labeling updates are needed at this time.

2 Drug Information

2.1 Drug

CAS Registry Number: 571190-30-2
Trade name: IBRANCE
Generic Name: Palbociclib
Code Name: PD-0332991
Chemical Name: 6-Acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one
Molecular Formula/Molecular Weight: $C_{24}H_{29}N_7O_2$/ 447.54 g/mole
Structure or Biochemical Description:



Pharmacologic Class: kinase inhibitor
Mechanism of action: an inhibitor of CDK 4/6
Relevant INDs, NDAs, BLAs and DMFs: IND 69,324,
NDA 207103 (capsule formulation)

2.2 Drug Formulation: tablet, 75 mg, 100 mg or 125 mg

2.3 Comments on Novel Excipients: none

2.5 Comments on Impurities/Degradants of Concern: refer to Brief Discussion of Nonclinical Findings (section 1.2) in this review

2.6 Proposed Clinical Population and Dosing Regimen

Refer to the approved label for IBRANCE®

3 Studies Submitted

Studies Reviewed

Toxicology

Repeat dose

	Title	
1	1-Month Oral Gavage Toxicity and Toxicokinetic Study with PD-0332991 in Rats	15LJ079

Reproductive and Developmental Toxicology Studies

	Title	
1	A Pre- and Postnatal Developmental Toxicity Study of PD-0332991 by Oral Gavage in Rats	15GR387

Studies Not Reviewed

Toxicology

Repeat dose

	Title	
1	1-Month Oral Gavage Toxicity Study of PD-0332991 in Sprague-Dawley Rats	17GR191

6 General Toxicology

Study title: 1-Month Oral Gavage Toxicity and Toxicokinetic Study with PD-332991 in Rats

Study no.: 15LJ079

Study report location:

Conducting laboratory and location: (b) (4)

Date of study initiation:

GLP compliance: yes

QA statement: yes (X) no ( )

Drug, batch #, and % purity:

Test Article	Description	Storage	Lot Number	Exit Testing Date	Purity
1	PD-0332991 plus (b) (4) (b) (4)	(b) (4)	00709888-251-02	26 January 2016	98.6%
2	PD-0332991 plus (b) (4) (b) (4)		00709888-244-02	26 January 2016	96.2%
3	PD-0332991 plus (b) (4) (b) (4)		00709888-253-01	26 January 2016	100.0%
4	PD-0332991 plus (b) (4) (b) (4)		00709888-250-01	26 January 2016	100.0%
5	PD-0332991 plus (b) (4) (b) (4)		00709888-257-02	26 January 2016	100.8%

Key study findings:

- Once daily oral administration of PD-0332991 with impurities for 1 month did not cause severe toxicity in rats at 10 mg/kg/day (males) or 200 mg/kg/day (females);
- Test article-related changes were limited to mild alterations in some hematology test parameters, decreased organ weight parameters (prostate, thymus, and spleen), and a microscopic finding of minimal hypocellular sternum marrow.
- The observed changes were generally similar for both sexes regardless of PD-0332991 dose or impurity content and were also consistent with the intended pharmacology of PD-0332991.
- No apparent effect of added impurities on systemic exposure of PD-0332991 were observed.

METHODS:

***Doses:**	10 mg/kg/day to male 200 mg/kg/day to female Other details see the table below (Experiment groups)
Frequency of dosing:	once daily for 28 days
Route of administration	Oral gavage
Dose volume	10 mL/kg
Formulation/Vehicle	0.5% (w/v) methylcellulose (4000 cps) in reverse osmosis water
Species/strain:	Crl:CD(SD) rats
Age	6 to 7 weeks old
Weight	Male: 157 to 252 g; Female: 135 to 180 g

Number/sex/group	10/sex/group
Satellite groups (TK)	3/sex/group
Unique study design	none
Deviation from study protocol	none

*Doses for this study were selected based on findings from a 15-week oral dose study of PD-0332991 (12LJ025). In that study, the no-observed-adverse-effect level (NOAEL) was assigned to the 10 and 200 mg/kg/day doses for males and females, respectively.

Experimental groups

Group[a]	Subgroup	No. of Animals		Dose[b] (mg/kg/day)		Dose Concentration[b] (mg/mL)	
		Male	Female	Male	Female	Male	Female
1 Control	1 (Toxicity)	10	10	0	0	0	0
	2 (Toxicokinetic)	3	3	0	0	0	0
2 Test Article 1 (PD-0332991 + (b) (4)	1 (Toxicity)	10	0	11	NA	1.1	NA
	2 (Toxicokinetic)	3	0	11	NA	1.1	NA
3 Test Article 2 (PD-0332991 + (b) (4)	1 (Toxicity)	10	0	10.3	NA	1.03	NA
	2 (Toxicokinetic)	3	0	10.3	NA	1.03	NA
4 Test Article 3 (PD-0332991 + (b) (4)	1 (Toxicity)	0	10	NA	245	NA	24.5
	2 (Toxicokinetic)	0	3	NA	245	NA	24.5
5 Test Article 4 (PD-0332991 + (b) (4)	1 (Toxicity)	0	10	NA	224	NA	22.4
	2 (Toxicokinetic)	0	3	NA	224	NA	22.4
6 Test Article 5 (PD-0332991 + (b) (4)	1 (Toxicity)	0	10	NA	200	NA	20
	2 (Toxicokinetic)	0	3	NA	200	NA	20

NA = Not applicable.

a Group 1 received vehicle control article only.

b The PD-0332991 dose and dose concentration for Groups 2-5 reflect adjustments based on the Calculation of Correction Factors table in order to achieve the target impurity concentration values. No adjustment (based on the correction factor) was made at the time of dose formulation preparation.

(Copied from the applicant's submission)

OBSERVATIONS AND TIMES:

Mortality	twice daily
Clinical Observations	1 hour postdose on each day of dosing
Detailed physical examinations	once during the acclimation phase and each toxicity animal prior to dosing on Days 1, 8, 15, 22, and 28 of the dosing phase
Body weights	once during the acclimation phase, and before dosing on Days 1, 8, 15, 22, and 28 of the dosing phase
Food consumption	weekly (based on Day 1 of the dosing phase) to Week 4 and from Day 22 to Day 28 of the dosing phase
Ophthalmoscopy	once during the acclimation phase for all animals and once for all toxicity animals during Week 4 of the dosing phase
Hematology and coagulation Serum chemistry	on the day of scheduled euthanasia (Day 29)
Urinalysis	on the day of scheduled euthanasia (day 29)
Gross pathology:	All animals at necropsy, on Day 29

Organ weights:	All animals at necropsy, on Day 29
Histopathology:	All animals at necropsy, on Day 29/30 (males/females) Adequate Battery: yes (x), no ( ) Peer review: yes (x), no ( )
Toxicokinetics:	Days 1 and 26 Collection Time Points: 1, 4, 7, and 24 hours postdose

RESULTS:

Mortality: none
Clinical signs: unremarkable

Bodyweight: unremarkable

Food consumption: unremarkable

Ophthalmoscopy: unremarkable

Hematology: All groups administered PD-0332991 and an impurity exhibited mildly lower red blood cell count (b) (4) control) and absolute reticulocyte count (0.78 to 0.85x control) and mildly higher mean corpuscular volume (b) (4) control), mean corpuscular hemoglobin (b) (4) control), and red cell distribution width (b) (4) control). All female groups administered PD-0332991 and an impurity exhibited mildly lower white blood cell count (b) (4) control) due to mildly lower absolute lymphocyte count (b) (4) control). Absolute large unstained cell count was also lower (b) (4) control) for all female groups administered PD-0332991 and an impurity.
Clinical Chemistry: unremarkable

Urinalysis: unremarkable

Gross Pathology: unremarkable

Organ Weights:

Table 1 Summary of organ weight

	Percentage deviation from control (n=12)									
	Absolute Organ Weight					Organ Weight/body Weight				
Sex	Male		Female			Male		Female		
Dose Group (mg/kg)	11	10.3	245	224	200	11	10.3	245	224	200
Thymus	-23*	-28*	-38*	-39*	-31*	-21	-27*	-35*	-35*	-28*
Spleen	-5	-7	-23*	-22*	-23*	-4	-5	-19*	-16*	-19*
Prostate	-8	-9*	-	-	-	-6	-16*	-	-	-

"-": not applicable ; *: P< 0.05

Histopathology: Minimal hypocellular marrow was present in the sternum of some animals in all dosed groups, with the exception of females administered test article 4 (PD-0332991 + (b) (4) % (b) (4)

Toxicokinetics:

Table 2 Mean Overall Toxicokinetic Parameters of PD-0332991 in Sprague Dawley Rat Plasma on Day 28

Dose (mg/kg)	Impurity	Sex	Cmax (ng/mL)	Cmax /Dose	AUC24 (hr.ng/mL)	AUC24 /Dose	Tmax (hr)
11.0	(b) (4)	M	444	40	4960	451	3
10.3		M	354	34	3920	381	4
245		F	608	2.5	6590	27	5
224		F	325	1.5	5010	22	2
200		F	409	2	5180	26	8

Study title: A Pre- and Postnatal Developmental Toxicity Study of PD-0332991 by Oral Gavage in Rats

Study no.:	
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 7, 2015
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	PD-0332991 lot # E010014255 (GR07475), 0.990 potency

Key study findings:

- At 300 mg/kg/day, PD-0332991-related adverse lower mean maternal (F0) body weight gain was noted during the gestation dosing phase ((b) (4) control for the interval of GD 6 to 20), which resulted in lower mean maternal (F0) body weights on GD 20 (b) (4) control).
- There were also PD-0332991-related adverse lower mean maternal (F0) food consumption at 300 mg/kg/day during the gestation dosing phase (b) (4) control for the interval of GD 6 to 21).
- There were no adverse effects on the F1 generation.

Methods

Doses:	0, 30, 100, 300 mg/kg
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% aqueous methylcellulose in reverse

osmosis (RO) deionized water
Species/Strain: Female Crl:CD(SD) Sprague Dawley rats
Number/Group: 22 pregnant females/group
Animal age: 60 to 70 days
Study design: Dosing once daily on GD 6 through LD 20 (rats assigned to natural delivery that delivered a litter) or GD 24 (the rat assigned to natural delivery that did not deliver a litter).
Deviation from study protocol: none

Experimental Design

Group No.	Test Material	Dose (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Number of F0 Female Rats (Assigned F0 Female Rat Numbers)
1	Vehicle Control Article	0	0	10	22 (3401-3422)
2	PD-0332991	30	3	10	22 (3423-3444)
3	PD-0332991	100	10	10	22 (3445-3466)
4	PD-0332991	300	30	10	22 (3467-3488)

Assigned F1 Generation Rat Numbers

Group No.	Number of F1 Rats (Assigned F1 Numbers)	
	F1 Male Rats	F1 Female Rats
1	1701-1722	1801-1822
2	1723-1744	1823-1844
3	1745-1766	1845-1866
4	1767-1788	1867-1888

Dosage Justification

Doses for this study were based on previous studies in pregnant rats at doses of 30, 100, and 300 mg/kg/day (Pfizer Reference Numbers 12LJ116 and 13GR062) and a fertility and early embryonic development study in female rats at doses of 30, 100 and 300 mg/kg/day (Pfizer Reference Number 13GR034). In the studies in pregnant rats, no toxicity was observed at ≤100 mg/kg/day and slight maternal toxicity (lower body weight gain and food consumption) and fetal toxicity (lower fetal weights) were observed at 300 mg/kg/day.

Observations and Results

Dose Formulation Analyses: All study samples analyzed had mean concentrations that were within or equal to the acceptance criteria of ± 15% (individual values within or equal to ± 20%) of their theoretical concentrations.

Maternal (F0)

Mortality: at least twice daily (AM and PM)

None

Clinical signs: general appearance daily, postdose observations were recorded between 1 and 2 hours after dose administration and again at the end of the normal working day, maternal behavior was recorded daily during the postpartum phase
unremarkable

Body weights: on the day of or after arrival, on GD 5, daily during the gestation dose phase (beginning on GD 6) and on LD 1, 4, 7, 10, 14, 18, and 21
Gestation Phase
≤ 100 mg/kg: unremarkable
300 mg/kg: ↓ mean BW for the interval of GD 6 to 20 (0.80x control)
↓ mean body weight gain for the interval of GD 6 to 9 and again at each tabulated interval between GD 12 to GD 20 (0.57x to 0.92x control). GD 6 to 9 and GD 18 to 20 reached statistical significance.
Lactation Phase
Unremarkable

Food consumption: on GDs 6, 9, 12, 15, 18, and 21, and on LD 1, 4, 7, 10, and 14.
Gestation Phase
300 mg/kg/day mean maternal food consumption was statistically significantly lower than the control group mean at each tabulated interval between GD 6 to GD 21 (0.86x to 0.92x control).
Lactation Phase
unremarkable

Natural Delivery and Litter Observations: adverse clinical signs, duration of gestation (GD 0 to the time the first pup was observed), litter size (defined as all pups delivered), and pup viability at birth.
There were no PD-0332991-related effects on any natural delivery parameter.
There were no PD-0332991-related effects on any litter parameter, including the lactation index.

Necropsy:

Group No.	No. of Animals	Scheduled Euthanasia Day	Necropsy Procedures				Histology	Histopathology
			Ovarian/ Uterine Examination	Necropsied	Tissues Collected	Organs Weighed		
1	22	LD 21	X	X	X[a]	-	-	-
2	22						-	-
3	22						-	-
4	22						-	-
Dam that did Not Deliver		GD 25	X	X	X[a]	-	-	-
Dams with No Surviving Pups		-	-	-	-	-	-	-
Unscheduled Deaths			-	-	-	-	-	-

X = Procedure conducted; - = Not applicable; GD = Gestation Day; LD = Lactation Day.
[a] See Section 4.13.4 (Tissue Collection and Preservation) for tissues that were collected and/or retained for possible future evaluation.

Unremarkable

Offspring (F1):
Preweaning
Mortality: at least twice daily and the pups in each litter were counted once daily,
None

Clinical observations: once daily
unremarkable

Body weights were recorded on Days 1 (birth), 4, 7, 10, 14, 18, and 21 postpartum
Unremarkable

Gross Pathology: pups on day 4 or 21 postpartum
Unscheduled Deaths: all pups, Days 1 to 21 Postpartum
Scheduled Euthanasia: on Days 4 and 21 postpartum, all pups not selected for continued observation
unremarkable

Postweaning
Mortality: at least twice daily
none

Clinical observations: at least once weekly
unremarkable

Body weights:
Male F1: once weekly, and on the day of scheduled euthanasia (male F1),
Female F1: once weekly during the postweaning phase, and on GDs 0, 7, 10, and 14
unremarkable

Food consumption: female only, at least weekly except during cohabitation and on GDs 0, 7, 10, and 14
unremarkable

Sexual Maturation
F1 females were evaluated once daily beginning on Day 28 postpartum and F1 males were evaluated once daily beginning on Day 35 postpartum.
Unremarkable

Behavioral Assessments
Motor Activity: Motor activity was evaluated in one F1 male and one female rat from each litter once on Day 60 postpartum ± 5 days.
Morris Water Maze: One F1 male and one female rat from each litter was evaluated for learning and retention of a spatial navigation task (water-filled Morris maze) beginning between 65 and 80 days postpartum.

Acoustic Startle Response: Acoustic startle habituation was evaluated on Days 80 to 90 postpartum.
unremarkable

Estrous Cycling, Mating, and Fertility: Estrous cycle evaluation samples were collected from F1 females for 14 consecutive days before initiation of cohabitation and then until spermatozoa were observed in a smear of the vaginal contents and/or a copulatory plug was observed in situ during cohabitation.
unremarkable

Necropsy Observations:
Male Rats: all F1 male rats after completion of the 14-day cohabitation period (Days 120 through 123 postpartum)
Female Rats: F1 female rats Ovarian and Uterine Examinations on GD 14
unremarkable

Toxicokinetics: not performed

13 Appendix/Attachments

none

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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