PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrIBRANCE™

Palbociclib capsules

75 mg, 100 mg and 125 mg capsules

Protein Kinase Inhibitor

"IBRANCE, 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, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for IBRANCE please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php"

IBRANCE, indicated in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy, has been issued marketing authorization without conditions.

Pfizer Canada Inc.
17300 Trans-Canada Highway
Kirkland, Quebec
H9J 2M5

Date of Preparation:
May 19, 2017

Submission Control No: 195948

This product has been authorized under the Notice of Compliance with Conditions (NOC/c)

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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[Pr]IBRANCE™

Palbociclib capsules

PART I: HEALTH PROFESSIONAL INFORMATION

"IBRANCE, 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 has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for IBRANCE please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php"

IBRANCE, indicated in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy, has been issued marketing authorization without conditions.

SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 75 mg, 100 mg, 125 mg	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

IBRANCE (palbociclib) is indicated:

NOC/c
- 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.
- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy. Pre- or perimenopausal women must also be treated with a luteinizing hormone releasing hormone (LHRH) agonist.

Geriatrics (≥ 65 years of age):
In clinical trials, of 84 patients who received IBRANCE plus letrozole, 37 patients (44%) were ≥65 years of age. Of 347 patients who received IBRANCE plus fulvestrant, 86 patients (25%) were ≥65 years of age. No overall differences in the efficacy of IBRANCE were observed between these patients and younger patients in either study. Neutropenia and leukopenia (all grades and Grades 3 and 4) were reported more frequently in patients ≥65 than in patients <65 years of age treated with IBRANCE plus letrozole, whereas similar incidences were reported for these parameters in both age groups for patients treated with IBRANCE plus fulvestrant .

Pediatrics (< 18 years of age):
Safety and efficacy of IBRANCE in children and adolescents <18 years have not been studied.

NOC/c CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

NOC/c WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

IBRANCE (palbociclib) should be prescribed and managed by a qualified physician who is experienced in the use of anti-cancer agents.

The following is a significant adverse drug reaction identified in clinical trials conducted with IBRANCE:

- Neutropenia (see **Hematologic** section below)

General

Effects on ability to drive and use machines
No studies of the effects of IBRANCE (palbociclib) on the ability to drive or operate machinery have been conducted. However, since fatigue and dizziness have been reported with the use of IBRANCE, patients should exercise caution when driving or operating machinery while taking IBRANCE.

Carcinogenesis and Mutagenesis
Carcinogenicity studies have not been conducted with IBRANCE.

Cardiovascular

Cardiac Electrophysiology

In the in vivo cardiovascular safety pharmacology studies conducted in dogs, QTc interval prolongation was highly correlated with the plasma exposure to palbociclib. An unbound plasma concentration of 67 ng/mL was associated with a 5 msec increase in QTc (approximately 4 times the unbound steady-state human C_{max}) (see **DETAILED PHARMACOLOGY**).

The effect of palbociclib on QTc was evaluated through a pharmacokinetic/pharmacodynamic analysis using data from 184 patients with advanced cancer. At the mean observed maximal steady-state palbociclib concentration following a therapeutic schedule (e.g., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days), the mean QTcS increase was 5.60 msec and the upper bound of the 1-sided 95% confidence interval (CI) was 8.72 msec. Clinically relevant QT prolongation due to palbociclib is unlikely. A dedicated ECG substudy is ongoing.

Hematologic

Neutropenia

Neutropenia was the most frequently reported adverse reaction in patients treated with IBRANCE plus letrozole (75%) or IBRANCE plus fulvestrant (83%). Grade 3 decreased neutrophil counts were observed in approximately half of all patients, and Grade 4 decreased neutrophil counts were observed in 5% and 11% of patients treated with IBRANCE in combination with letrozole or fulvestrant, respectively [see **ADVERSE REACTIONS**].

The median time to first episode of any grade neutropenia was 15 days, and the median duration of Grade ≥3 neutropenia was 7 days.

Febrile neutropenia has been reported in about 1% of patients treated with IBRANCE plus fulvestrant, and has not been reported in patients treated with IBRANCE plus letrozole. One patient treated with IBRANCE plus fulvestrant died due to neutropenic sepsis. Physicians should inform patients to promptly report any episodes of fever.

Monitor complete blood count prior to the start of IBRANCE therapy, at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**]. Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia [see **DOSAGE AND ADMINISTRATION**]. For patients who experience Grade 3 neutropenia, consider repeating complete blood count monitoring one week later.

Other Hematologic Parameters

Decreases in leukocytes and platelets were observed in patients treated with either IBRANCE plus letrozole or IBRANCE plus fulvestrant. Grade 3 leukopenia was reported in 19% of IBRANCE plus letrozole patients and in 30% of IBRANCE plus fulvestrant patients. Decreased hemoglobin and lymphocytes were also observed in IBRANCE plus letrozole-treated patients [see **ADVERSE REACTIONS**].

Anemia and leukopenia were usually managed with temporary IBRANCE discontinuation and/or dose reduction. Monitor complete blood count prior to the start of IBRANCE therapy, at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated [see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION**].

Immune

Infections
IBRANCE may predispose patients to infections. Infections have been more frequently reported in patients treated with IBRANCE plus letrozole (55%) and in patients treated with IBRANCE plus fulvestrant (47%) than those treated in the respective comparator arms (34% and 31%, respectively). Grade ≥3 infections occurred in 5% of patients treated with IBRANCE plus letrozole and in no patients treated with letrozole alone. Grade ≥3 infections occurred in 3% of patients treated with either IBRANCE plus fulvestrant or placebo plus fulvestrant. Monitor patients for signs and symptoms of infection and treat as medically appropriate (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**). Physicians should be aware of the increased risk of infection with IBRANCE and should inform patients to promptly report any episodes of fever.

Respiratory

Pulmonary Embolism
Pulmonary embolism has been reported in 5% of patients treated with IBRANCE plus letrozole and in 1% of patients treated with IBRANCE plus fulvestrant. There were no cases of pulmonary embolism in patients treated either with letrozole alone or placebo plus fulvestrant. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

Drug-Drug Interactions

CYP3A inhibitors: Concomitant use of IBRANCE and CYP3A inhibitors (e.g. clarithromycin, itraconazole, ritonavir, ketoconazole, grapefruit or grapefruit juice) may increase exposure to palbociclib. In patients receiving IBRANCE, coadministration of a strong CYP3A inhibitor should be avoided (see DRUG INTERACTIONS).

CYP3A substrates: Concomitant use of IBRANCE and a CYP3A substrate may increase exposure to the CYP3A substrate. Caution is warranted when IBRANCE is co-administered with CYP3A substrates of narrow therapeutic index, such as alfentanil, cyclosporine, dihydroergotamine, or ergotamine (see DRUG INTERACTIONS).

CYP3A inducers: Concomitant use of IBRANCE and CYP3A inducers (e.g. strong inducers such as rifampin, carbamazepine, phenytoin, St John's Wort, and moderate inducers such as nafcillin, bosentan, modafinil) may decrease palbociclib plasma concentration. In patients receiving IBRANCE, coadministration of strong CYP3A inducers should be avoided (see **DRUG INTERACTIONS**).

Sexual Function/Reproduction

No clinical data have been obtained on fertility in humans. There were no effects on estrous cycle or mating and fertility in female rats in nonclinical studies [see ***Special Populations***]. Based on nonclinical safety findings, male fertility may be impaired by treatment with IBRANCE [see **PART II TOXICOLOGY, Reproductive and Developmental Toxicity**]. Men should consider sperm preservation prior to beginning therapy with IBRANCE [see ***Special Populations***].

Special Populations:

Pregnant Women: There are no adequate and well-controlled studies using IBRANCE in pregnant women.

IBRANCE may cause fetal harm when administered to a pregnant woman. In animal studies, palbociclib was shown to be fetotoxic in pregnant rats and rabbits [see PART II TOXICOLOGY].

IBRANCE should not be used during pregnancy and is indicated for use in postmenopausal women. If IBRANCE is used in women of childbearing potential, advise the patient to avoid becoming pregnant. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. If females of childbearing potential are receiving this drug they should use adequate contraceptive methods during therapy and for at least 21 days after completing therapy.

Nursing Women: It is not known whether palbociclib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IBRANCE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the patient.

Pediatrics (< 18 years of age): The safety and efficacy of IBRANCE in children and adolescents <18 years have not been studied.

Geriatrics (≥ 65 years of age): Population pharmacokinetic analysis was performed on data from 183 patients with cancer in an age range from 22 to 89 years. There was no clinically important difference in palbociclib exposure in patients ≥65 years of age compared with patients <65 years of age. In IBRANCE plus letrozole-treated patients, all grade neutropenia and leukopenia were reported more frequently in patients ≥65 years of age than in those <65 years of age (neutropenia: 81% vs. 70%, respectively; Grade 3/4: 57% vs. 52%; leukopenia: 54% vs. 35%, respectively), whereas similar incidences were reported for these parameters in both age groups in patients treated with IBRANCE plus fulvestrant.

Hepatic Impairment: Based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment, mild hepatic impairment had no

effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment.

Renal Impairment: Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment or requiring hemodialysis.

Monitoring and Laboratory Tests

Patients treated with IBRANCE should be monitored for signs and symptoms of myelosuppression, infection, and pulmonary embolism. Dose modification may be required [see **Dosage and Administration]**.

Monitor complete blood count prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first two cycles, and as clinically indicated.

For patients who experience Grade 3 neutropenia, consider repeating complete blood count monitoring one week later. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables [see **Dosage and Administration**].

NOC/c **ADVERSE REACTIONS**

Adverse Drug Reaction Overview
The safety of IBRANCE has been assessed in 2 randomized studies of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The most common adverse drug reactions of any grade reported in ≥10% of patients receiving palbociclib in combination with endocrine treatment were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, thrombocytopenia, diarrhea, alopecia, vomiting, decreased appetite, and rash.

Most patients treated with IBRANCE (palbociclib) experienced myelosuppressive effects with over half experiencing Grade 3 neutropenia at some point during treatment. Thrombocytopenia and anemia were less commonly observed. Myelosuppressive effects can be expected to occur from Cycle 1 forward.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Randomized Phase 2 Study (PALOMA-1)

The safety of IBRANCE (125 mg/day for 21 consecutive days followed by 7 days off treatment) plus letrozole (2.5 mg/day) versus letrozole alone was evaluated primarily in a randomized, controlled, Phase 2 trial (PALOMA-1). The data described below reflect exposure to IBRANCE in 83 out of 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE in the Phase 2 portion of PALOMA-1. Patients were randomized 1:1 to receive the combination IBRANCE plus letrozole versus letrozole alone.

The most common (>10%) adverse drug reactions of any grade reported in patients in the IBRANCE plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.

The most frequently reported serious adverse events in patients receiving IBRANCE plus letrozole were pulmonary embolism (5%) and diarrhea (2%).

Discontinuation and dose reduction due to AEs

Dose reductions due to an adverse event of any grade occurred in 39% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole.

Permanent discontinuation due to an adverse event occurred in 12 of 83 (15%) patients receiving IBRANCE plus letrozole, and in 2 of 77 (3%) patients receiving letrozole alone.

Treatment-emergent adverse events presented in Table 1 below are based on a median duration of treatment of 13.8 months for patients on the IBRANCE plus letrozole arm, and 7.6 months for patients on the letrozole alone arm.

Table 1. Adverse Reactions Reported for Patients Who Received IBRANCE plus Letrozole or Letrozole Alone in PALOMA-1

System Organ Class Any Adverse Drug Reaction	IBRANCE + Letrozole (N=83) All Grades %	 Grade 3 %	 Grade 4 %	Letrozole Alone (N=77) All Grades %	 Grade 3 %	 Grade 4 %
Infections and infestations						
URI[a]	31	1	0	18	0	0
Blood and lymphatic system disorders						
Neutropenia	75	48	6	5	1	0
Leukopenia	43	19	0	3	0	0
Anemia	35	5	1	7	1	0
Thrombocytopenia	17	2	0	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	7	0	0
Nervous system disorders						
Peripheral neuropathy[b]	13	0	0	5	0	0
Dysgeusia	7	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis[c]	25	0	0	7	1	0
Nausea	25	2	0	13	1	0
Diarrhea	21	4	0	10	0	0
Vomiting	15	0	0	4	1	0
Skin and subcutaneous tissue disorders						
Alopecia	22	N/A	N/A	3	N/A	N/A
General disorders and administration site conditions						
Fatigue	41	2	2	23	1	0
Asthenia	13	2	0	4	0	0
Pyrexia	8	0	0	3	0	0
Median duration of treatment (months)		14			8	

Grading according to CTCAE 3.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of subjects; N/A=not applicable; PT=preferred term; URI=Upper respiratory infection.

[a] URI includes the following PTs: Influenza, Influenza like illness, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection.

[b] Peripheral neuropathy includes the following PTs: Neuropathy peripheral, Peripheral sensory neuropathy.

[c] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

Abnormal Hematologic and Clinical Chemistry Findings

Table 2. Incidence of Hematology Laboratory Abnormality for Patients Who Received IBRANCE Plus Letrozole or Letrozole Alone in PALOMA-1

Laboratory Abnormality	IBRANCE + Letrozole (N=83)			Letrozole Alone (N=77)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
White blood cells decreased	95	44	0	26	0	0
Neutrophils decreased	94	57	5	17	3	0
Lymphocytes decreased	81	17	1	35	3	0
Hemoglobin decreased	83	5	1	40	3	0
Platelets decreased	61	3	0	16	3	0

N=number of subjects.

Randomized Phase 3 Study (PALOMA-3)

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in a randomized, controlled, Phase 3 trial (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative metastatic breast cancer who received at least 1 dose of IBRANCE in PALOMA-3. Patients were randomized 2:1 to receive the combination IBRANCE plus fulvestrant versus placebo plus fulvestrant.

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus fulvestrant arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported serious adverse reactions in patients receiving IBRANCE plus fulvestrant were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%).

Adverse reactions reported in patients who received IBRANCE plus fulvestrant or placebo plus fulvestrant in PALOMA-3 are listed in Table 3.

Discontinuation and dose reduction due to AEs

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus fulvestrant. No dose reduction was allowed for fulvestrant in PALOMA-3.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving IBRANCE plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for those patients receiving IBRANCE plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

Treatment-emergent adverse events presented in Table 3 below are based on a median duration of treatment of approximately 5 months for patients on the IBRANCE plus fulvestrant arm, and approximately 4 months for patients on the placebo plus fulvestrant arm.

Table 3. Adverse Events* Reported (With a Frequency of ≥5% on the IBRANCE Arm) for Patients Who Received IBRANCE Plus Fulvestrant or Placebo Plus Fulvestrant in PALOMA-3

Adverse Reaction	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	34	1	<1	24	2	0
Blood and lymphatic system disorders						
Neutropenia[b]	79	53	9	4	0	<1
Leukopenia[c]	46	25	<1	4	0	1
Anemia[d]	26	3	0	10	2	0
Thrombocytopenia[e]	19	2	<1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	13	<1	0	8	0	0
Psychiatric disorders						
Insomnia	11	<1	0	7	0	0
Nervous system disorders						
Headache	21	<1	0	17	0	0
Dysgeusia	6	0	0	2	0	0
Dizziness	11	<1	0	9	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	6	0	0	1	0	0
Cough	13	0	0	11	0	0
Dyspnoea	7	0	0	4	0	0
Gastrointestinal disorders						
Nausea	29	0	0	26	<1	0
Stomatitis[f]	25	<1	0	11	0	0
Diarrhea	19	0	0	17	<1	0
Constipation	17	0	0	14	0	0
Vomiting	15	<1	0	12	<1	0
Abdominal Pain	6	<1	0	5	0	0
Skin and subcutaneous tissue disorders						
Alopecia	15	N/A	N/A	6	N/A	N/A
Rash[g]	14	<1	0	5	0	0
General disorders and administration site conditions						
Fatigue	38	2	0	27	1	0
Asthenia	7	0	0	5	1	0
Pyrexia	9	<1	0	4	0	0
Oedema peripheral	8	0	0	5	0	0
SOC Investigations						
Aspartate aminotransferase increased	6	2	0	5	1	0

* Adverse events reported with a frequency of ≥5% on the IBRANCE arm and a higher frequency on the IBRANCE arm compared to the placebo arm
Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.
a Infections includes any reported PTs that are part of the System Organ Class Infections and infestations.
b Neutropenia includes: neutropenia and neutrophil count decreased
c Leukopenia includes: leukopenia and white blood cell count decreased
d Anemia includes: anaemia, haemoglobin decreased, and hematocrit decreased
e Thrombocytopenia includes: thrombocytopenia and platelet count decreased
f Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
g Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <5% of patients receiving IBRANCE plus fulvestrant in Study PALOMA-3 included dry skin (4.9%), Vision blurred (4.9%), alanine aminotransferase increased (4.6%), lacrimation increased (4.3%), dry eye (2.9%), and febrile neutropenia (0.6%).

Abnormal Hematologic and Clinical Chemistry Findings

Table 4. Incidence of Hematology Laboratory Abnormality for Patients Who Received IBRANCE Plus Fulvestrant or Placebo Plus Fulvestrant in PALOMA-3

Laboratory Abnormality	IBRANCE + Fulvestrant (N=345)			Placebo Plus Fulvestrant (N=172)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
White blood cells decreased	98	40	1	22	0	<1
Neutrophils decreased	95	53	9	11	0	1
Anemia	76	3	0	36	2	0
Platelets decreased	57	2	1	8	0	0

N=number of subjects.

Updated safety data for patients on the IBRANCE plus fulvestrant arm, based on an approximate 6-month increase in the median duration of treatment, were generally consistent with the safety table provided in Tables 3 and 4. No new safety concerns have been identified.

DRUG INTERACTIONS

Overview

Palbociclib is a substrate and weak inhibitor of CYP3A. It is also a moderate substrate of P-glycoprotein (P-gp) in vitro. Drug interactions were observed when IBRANCE (palbociclib) was coadministered with a strong CYP3A inhibitor and a strong CYP3A inducer. The aqueous solubility of palbociclib is pH-dependent. Drug interaction was observed when IBRANCE was coadministered with proton pump inhibitors (PPIs) under fasted conditions but was limited when IBRANCE was coadministered with PPIs under fed conditions. Food intake reduced the variability of palbociclib exposure. In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

Drug-Drug Interactions

Agents that may increase palbociclib plasma concentrations

CYP3A Inhibitors*:* Data from a study in 12 healthy subjects indicate that coadministration of multiple 200 mg daily doses of itraconazole with a single 125 mg IBRANCE dose increased palbociclib total exposure (area under the curve, AUC_{inf}) and the peak exposure (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125-mg IBRANCE dose given alone. The concomitant use of strong CYP3A inhibitors including, but are not limited to: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided.

Agents that may decrease palbociclib plasma concentrations

CYP3A Inducers*:* Data from a study in 14 healthy subjects indicated that coadministration of multiple 600 mg doses of rifampin, a strong CYP3A inducer, with a single 125 mg IBRANCE dose decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125 mg IBRANCE dose given alone. The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's wort, should be avoided.

Data from a drug interaction study in healthy subjects (N=14) indicated that coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg IBRANCE dose decreased palbociclib AUC_{inf} and C_{max} by 32% and 11%, respectively, relative to a single 125 mg IBRANCE dose given alone. If concomitant use of IBRANCE with moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) cannot be avoided, no dosing adjustments are required for IBRANCE.

Antacids*:* Data from a study in healthy subjects indicated that coadministration of a single 125 mg dose of IBRANCE with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease) compared with a single dose of IBRANCE administered alone. Given the reduced

effect on gastric pH of H2 receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid reducing agents on palbociclib exposure under fed conditions is expected to be minimal.

Data from another study in healthy subjects indicated that coadministration of a single 125 mg dose of IBRANCE with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with a single dose of IBRANCE administered alone.

IBRANCE should be taken with food.

Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

CYP3A Substrates: Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state in humans. In a study in 26 healthy subjects, coadministration of midazolam with multiple doses of IBRANCE increased the midazolam AUC_{inf} and the C_{max} values by 61% and 37%, respectively, as compared with administration of midazolam alone.

The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced as IBRANCE may increase their exposure.

Luteinizing Hormone Releasing Hormone (LHRH) Agonists
Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and goserelin when the 2 drugs were coadministered. Drug-drug interaction studies between palbociclib and other LHRH agonists have not been performed.

In vitro studies with transporters
In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 at clinically relevant concentrations.

In vitro studies demonstrate that palbociclib is not a substrate of OATP1B1 or OATP1B3.

Drug-Food Interactions
Grapefruit, grapefruit juice, and products containing grapefruit extract may increase palbociclib plasma concentrations and should be avoided.

The effect of food on palbociclib exposure was evaluated in healthy subjects. Compared to IBRANCE given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after IBRANCE dosing. In addition, food intake significantly reduced the inter-subject and intra-subject variability of palbociclib exposure. Based on these results, IBRANCE should be taken with food.

Drug-Herb Interactions
Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4/5 that may decrease palbociclib plasma concentrations and should be avoided.

Drug-Laboratory Interactions
Interactions between IBRANCE and laboratory tests have not been studied.

Drug-Lifestyle Interactions
Interactions between IBRANCE and lifestyle have not been studied.

NOC/c

DOSAGE AND ADMINISTRATION

Dosing Considerations
Pre/perimenopausal women treated with the combination IBRANCE plus fulvestrant therapy should be treated with luteinizing hormone releasing hormone (LHRH) agonists according to local clinical practice.

Recommended Dose and Dosage Adjustment
The recommended dose of IBRANCE (palbociclib) is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

IBRANCE should be taken with food. Patients should be advised to take their dose at approximately the same time each day.

Continue the treatment as long as the patient is deriving clinical benefit from therapy.

IBRANCE is used in combination with letrozole or fulvestrant. For full dosing instructions of letrozole or fulvestrant, please consult the corresponding Product Monographs.

Management of some adverse reactions may require temporary dose interruptions/delays and/or dose reductions, or permanent discontinuation of IBRANCE as per dose reduction schedules provided in Table 5, 6 and 7.

Table 5. IBRANCE Recommended Dose Modification for Adverse Events

Dose Level	Dose
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

*If further dose reduction below 75 mg/day is required, discontinue palbociclib treatment.

Table 6. Dose Modification and Management – Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated.	
CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: Withhold IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the *same dose*. Day 14 of first 2 cycles: Continue IBRANCE at current dose to complete cycle. Repeat complete blood count on Day 21. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles.
Grade 3 neutropenia[b] with fever ≥38.5 ºC and/or infection	Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.
Grade 4	Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.

Grading according to CTCAE 4.0
CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.
[a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b] Absolute neutrophil count (ANC): Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3.

Table 7. IBRANCE Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next reduced dose level.

Grading according to CTCAE 4.0
CTCAE=Common Terminology Criteria for Adverse Events. [b.]

No dose adjustments are required on the basis of age, gender, or body weight [see **Special Populations**].

Missed Dose
If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Special populations

Hepatic impairment: No dose adjustments are required for patients with mild hepatic impairment (total bilirubin ≤upper limit of normal (ULN) and aspartate transaminase (AST) >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST). IBRANCE has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see **Pharmacokinetics, *Special Populations and Conditions***].

Renal impairment: No dose adjustments are required for patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min). IBRANCE has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or requiring hemodialysis [see **Pharmacokinetics, *Special Populations and Conditions***].

OVERDOSAGE

There is no known antidote for IBRANCE (palbociclib). The treatment of overdose of IBRANCE should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Palbociclib is a selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. Through inhibition of cyclin D-CDK4/6 complex activity, palbociclib inhibits the phosphorylation of retinoblastoma (Rb) protein, blocking cell cycle progression from G1 into S phase. In a panel of molecularly profiled breast cancer cell lines, palbociclib exhibited the greatest efficacy towards the luminal ER-positive subtype; particularly, in cell lines with increased Rb and cyclin D1 and decreased p16 gene expression. In combination with anti-estrogen agents, palbociclib demonstrated enhanced inhibition of cell proliferation and induction of cell senescence in ER-positive breast cancer models.

Pharmacodynamics

A pharmacokinetic/pharmacodynamic analysis was conducted using data from 184 patients with advanced cancer to evaluate the relationship between heart rate corrected QT interval according to study-specific criteria (QTcS) and palbociclib concentration. A positive correlation was observed between QTcS and palbociclib concentration, with a mean QTcS increase of 5.60 msec, and upper bound 1-sided 95% confidence interval of 8.72 msec at the mean observed maximal steady-state palbociclib concentration following a therapeutic schedule (i.e., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days).

Pharmacokinetics

The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects. Pharmacokinetic parameters of palbociclib and letrozole obtained from study A5481003 are shown in Table 8.

Table 8 Summary of Plasma Pharmacokinetic Parameters of Palbociclib (125 mg QD) and Letrozole (2.5 mg QD) at Steady State When Administered Alone or in Combination to Patients with Advanced Breast Cancer in the Phase 1 Portion of A5481003

Palbociclib PK Parameter Summary Statistics[a]						
Treatment	**C_{max} (ng/mL)**	**$AUC_{(0-24)}$ (ng.hr/mL)**	**Tmax (hr)**	**$t_{½}$ (hr)**	**CL/F (L/hr)**	**V_zF (L)**
PLB alone (N=12)	116 (28)	1982 (29)	7.9 (2.2-8.2)	28.8 (±5.0)	63.1 (29)	2583 (26)
PLB + LTZ (N=12)	108 (29)	1933 (31)	7.9 (2.0-8.1)	-	-	-
Letrozole PK Parameter Summary Statistics[a]						
LTZ alone (N=12)	104 (31)	1936 (35)	1.0 (0-4.4)	-	-	-
LTZ + PLB (N=12)	95.0 (27)	1739 (30)	2.0 (0.8-4.1)	-	-	-

$AUC_{(0-24)}$=area under the plasma concentration-time curve from time 0 to 24 hours after dosing;
CL/F=apparent oral clearance; C_{max}=maximum observed plasma concentration; CSR=Clinical Study Report;
%CV=percent coefficient of variation; LTZ=letrozole; N=total number of patients in the treatment arm;
PK=pharmacokinetic; PLB=Palbociclib; QD=once daily; Std Dev=standard deviation; T_{max}=time to first occurrence of C_{max};
$t_{1/2}$=terminal plasma half-life; V_z/F=apparent volume of distribution.
a. Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for T_{max} and arithmetic mean (±Std Dev) for $t_{1/2}$.

Absorption: Following oral single-dose administration, palbociclib was absorbed with median time to achieve C_{max} of 4 to 8 hours. The mean absolute bioavailability of IBRANCE after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulated with a median accumulation ratio of 2.4 (range 1.5-4.2).

Food effect: The effect of food on palbociclib exposure was evaluated in healthy subjects. Compared to IBRANCE given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before

and 2 hours after IBRANCE dosing. In addition, food intake significantly reduced the inter-subject and intra-subject variability of palbociclib exposure. Based on these results, IBRANCE should be taken with food.

Proton pump inhibitors effect:
In a healthy subject study, coadministration of a single dose of IBRANCE with the PPI rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease), when compared to a single dose of IBRANCE administered alone.

In another healthy subject study, coadministration of a single dose of IBRANCE with the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared to a single dose of IBRANCE administered alone.

Distribution: Binding of palbociclib to human plasma proteins in vitro was ~85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The geometric mean apparent volume of distribution (V_z/F) was 2583 L.

Metabolism: In vitro and in vivo studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [^{14}C]palbociclib to humans, the major primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23% of total radioactivity in plasma). The major circulating metabolite was a glucuronide conjugate of palbociclib (14.8% of total radioactivity in plasma), although it only represented 1.5% of the administered dose in the excreta. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 25.8% of the administered dose. In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulfotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Excretion: The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.08 L/hr, and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{14}C]palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. The majority of the material was excreted as metabolites. Excretion of unchanged palbociclib in feces and urine was 2.3% and 6.9% of the administered dose, respectively.

Special Populations and Conditions:

Age, Gender, and Body Weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 to 123 kg), sex had no effect on the exposure of palbociclib, and neither age nor body weight had a clinically important effect on the exposure of palbociclib.

Pediatric Use

Pharmacokinetics of palbociclib have not been evaluated in children and adolescents <18 years of age.

Hepatic Impairment

Based on a population pharmacokinetic analysis that included 183 patients with cancer, where 40 patients had mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Renal Impairment

Based on a population pharmacokinetic analysis that included 183 patients with cancer, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), neither mild nor moderate renal impairment had an effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment or requiring hemodialysis. About 17.5% of IBRANCE and its metabolites are excreted via the kidney.

Japanese population

Data from a pharmacology study evaluating the effect of Japanese ethnicity on the PK of a single 125-mg oral palbociclib dose given to Japanese and non-Asian healthy volunteers indicate that palbociclib AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects when compared with non-Asian subjects.

STORAGE AND STABILITY

Store at 20°C to 25°C; excursions permitted between 15°C to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Any unused product or waste material should be disposed in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

IBRANCE (palbociclib) is supplied in the following strengths and package configurations:

IBRANCE Capsules		
Package Configuration	**Capsule Strength (mg)**	**Capsule Description**
Bottles of 21 capsules	125	opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink "Pfizer" on the cap, "PBC 125" on the body
Bottles of 21 capsules	100	opaque, hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink "Pfizer" on the cap, "PBC 100" on the body
Bottles of 21 capsules	75	opaque, hard gelatin capsules, size 2, with light orange cap and body, printed with white ink "Pfizer" on the cap, "PBC 75" on the body

List of excipients

Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells. The light orange, light orange/caramel and caramel opaque capsule shells contain gelatin, red iron oxide, yellow iron oxide, and titanium dioxide; and the printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

PART II: SCIENTIFIC INFORMATION

"IBRANCE, 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 has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for IBRANCE please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php"

IBRANCE, indicated in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy, has been issued marketing authorization without conditions.

PHARMACEUTICAL INFORMATION

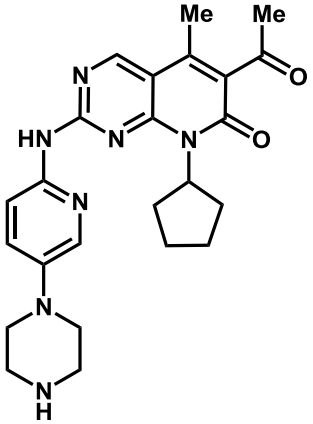
Drug Substance

Common name: Palbociclib

Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Molecular formula and molecular mass: $C_{24}H_{29}N_7O_2$, 447.54 Daltons

Structural formula:



Palbociclib is a yellow to orange powder with pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.

CLINICAL TRIALS

NOC/c *PALOMA-1: IBRANCE in combination with letrozole*

The efficacy of IBRANCE (palbociclib) was evaluated in a randomized, open-label, multicenter Phase 2 study A5481003 (PALOMA-1) of IBRANCE plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. The study population was further enriched with patients who had genomic amplification of cyclin D1 and/or loss of p16 (biomarker-positive patients). This study was not designed as a registrational trial and included several data-driven protocol amendments. Patients (N=165) were randomized and stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease).

Patients receiving letrozole alone did not cross over to the combination at the time of progression.

The patient demographic and baseline characteristics were similar between the study arms as shown in Table 9 below.

Table 9. Summary of Demographic and Baseline Characteristics by Treatment – PALOMA-1 (Intent-to-Treat Population)

Parameter	IBRANCE + Letrozole (N=84)	Letrozole (N=81)
Age (years)		
Median (min, max)	62.5 (41, 89)	64.0 (38, 84)
<65 [n (%)]	47 (56.0)	42 (51.9)
≥65 [n (%)]	37 (44.0)	39 (48.1)
Race [n (%)]		
White	76 (90.5)	72 (88.9)
Black	1 (1.2)	1 (1.2)
Asian	6 (7.1)	4 (4.9)
Other	1 (1.2)	4 (4.9)
ECOG performance status [n (%)]		
0	46 (54.8)	45 (55.6)
1	38 (45.2)	36 (44.4)
Disease site* [n (%)]		
Visceral	39 (46.4)	40 (49.4)
Bone only	17 (20.2)	14 (17.3)
Other	28 (33.3)	27 (33.3)
Disease-free interval* [n (%)]		
>12 months from the end of adjuvant treatment to disease recurrence	37 (44.1)	36 (44.4)
≤12 months from the end of adjuvant treatment to disease recurrence and de novo advanced disease	47 (56.0)	45 (55.6)
Current disease stage [n (%)]		
Stage IIIB (locally advanced)	2 (2.4)	1 (1.2)
Stage IV (metastatic)	82 (97.6)	80 (98.8)
Prior systemic therapy [n (%)]		
No	44 (52.4)	37 (45.7)
Yes	40 (47.6)	44 (54.3)
Chemotherapy [n (%)]	34 (40.5)	37 (45.7)
Anthracycline	26 (31.0)	25 (30.9)
Taxane	12 (14.3)	14 (17.3)
Other	34 (40.5)	37 (45.7)
Antihormonal therapy [n (%)]	27 (32.1)	28 (34.6)
Tamoxifen	24 (28.6)	24 (29.6)
Aromatase inhibitor	14 (16.7)	12 (14.8)
Anastrozole	8 (9.5)	11 (13.6)
Exemestane	4 (4.8)	2 (2.5)
Letrozole	2 (2.4)	1 (1.2)
Other [n (%)]	2 (2.4)	0

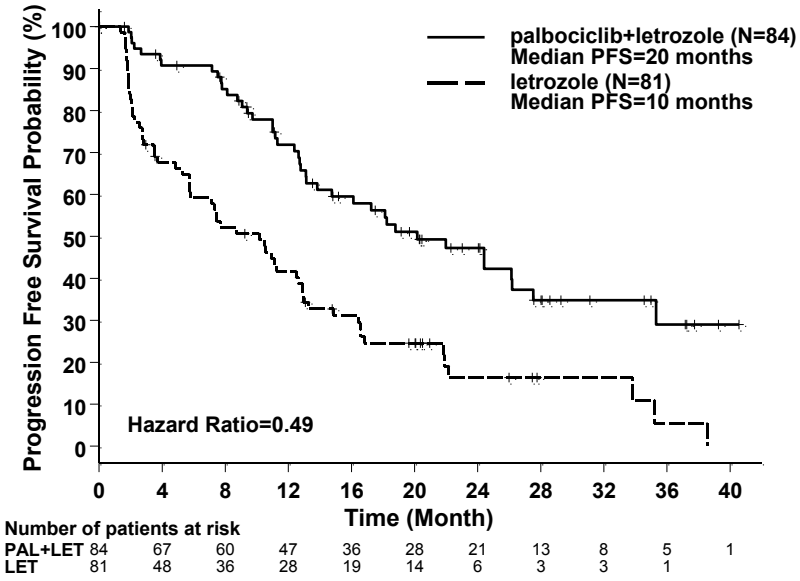
*Based on randomization.
Abbreviations: ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; N=number of patients; n=number of patients in subgroup.

The primary endpoint of the study was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors 1.0 (RECIST). Due to data-driven protocol amendments, statistical inference is not possible; therefore, p-values and 95% confidence intervals are not presented.

The median PFS for patients in the IBRANCE plus letrozole arm was 20 months, and 10 months for patients in the letrozole alone arm. The observed hazard ratio (HR) was 0.49 in favor of IBRANCE plus letrozole.

The primary efficacy results were obtained from the final PFS analysis of all patients randomized to the Phase 2 study (see Table 10 and Figure 1).

Figure 1. Kaplan-Meier Curves of Progression-Free Survival – PALOMA-1 (Investigator Assessment, Intent-to-Treat Population)



LET=letrozole; N=number of subjects; PAL=palbociclib; PFS=progression-free survival.

The treatment effect of the combination on PFS was also supported by a retrospective blinded, independent central review (BICR) of radiographs from all randomized Phase 2 patients, with an observed HR of 0.62 in favor of IBRANCE plus letrozole. This analysis also identified the possibility of investigator bias, based on discordance rates that were different between treatment arms.

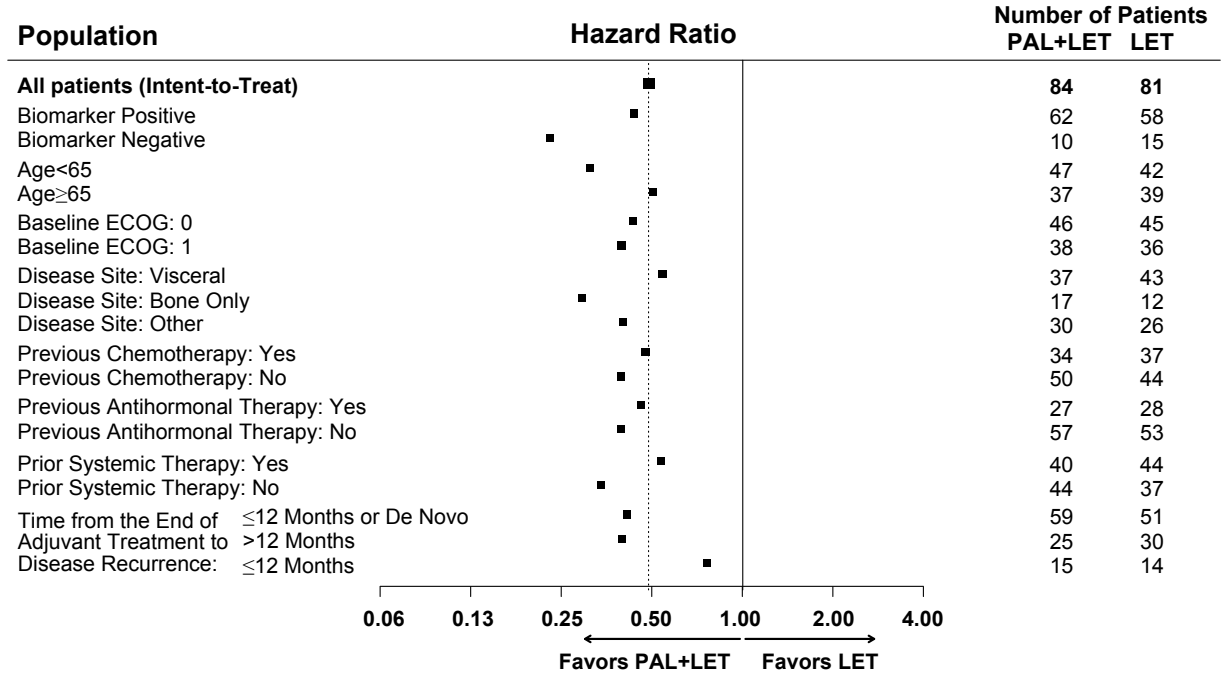
At the time of final analysis of PFS, overall survival (OS) data was not mature, with events having been reported for only 37% of patients.

Table 10. Efficacy Results - PALOMA-1 (Investigator Assessment, Intent-to-Treat Population)

Endpoint	IBRANCE + Letrozole (N=84)		Letrozole (N=81)
PFS (Median [months]) Investigator assessed	20		10
Hazard ratio		0.49	
PFS (Median [months]) BICR assessed	26		15
Hazard ratio		0.62	
ORR[a]	55%		39%

ORR=objective response rate; PFS=progression free survival.[a] ORR, defined as number (%) of patients with complete response or partial response, was analyzed in the evaluable patients with measurable disease at baseline (IBRANCE plus letrozole N=65; letrozole alone N=66).

Figure 2. Primary and Subgroup Analyses of Investigator-Assessed Progression-Free Survival With Stratification and Key Prognostic Factors per CRF: Intent-to-Treat Population



ECOG= Eastern Cooperative Oncology Group; PAL = palbociclib; LET = letrozole.

PALOMA-3: IBRANCE in combination with fulvestrant

The efficacy of IBRANCE plus fulvestrant versus placebo plus fulvestrant was evaluated in an international, randomized, double-blind, parallel-group, multicenter study (PALOMA-3) conducted in women with HR-positive and HER2-negative locally advanced or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy.

A total of 521 pre and postmenopausal women were randomized 2:1 to IBRANCE plus fulvestrant or placebo plus fulvestrant and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases.

IBRANCE was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Fulvestrant 500 mg was administered to all patients as described in its Product Monograph. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of PALOMA-3. Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Baseline demographics and prognostic characteristics of the study population are shown in Table 11 below.

Table 11. Summary of Demographic and Other Baseline Characteristics PALOMA-3 (Intent-to-Treat Population)

Characteristics	IBRANCE + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Age (years)		
Median (min-max)	57 (30-88)	56 (29-80)
<65, n (%)	261 (75.2)	131 (75.3)
≥65, n (%)	86 (24.8)	43 (24.7)
Race, n (%)		
White	252 (72.6)	133 (76.4)
Black	12 (3.5)	8 (4.6)
Asian	74 (21.3)	31 (17.8)
Other	8 (2.3)	1 (0.6)
Unspecified	1 (0.3)	1 (0.6)
ECOG performance status, n (%)		
0	206 (59.4)	116 (66.7)
1	141 (40.6)	58 (33.3)
Documented sensitivity to prior hormonal therapy,[a] n (%)		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)
Visceral metastases,[a] n (%)		
Yes	206 (59.4)	105 (60.3)
No	141 (40.6)	69 (39.7)
Menopausal status,[a,b] n (%)		
Pre-/peri-	72 (20.7)	36 (20.7)
Post-	275 (79.3)	138 (79.3)
Extent of Disease		
Locally advanced	69 (19.9)	47 (27.0)
Metastatic	86 (24.8)	36 (20.7)
Prior systemic therapies, n (%)		
No	0 (0)	0 (0)
Yes	347 (100)	174 (100)
Number of regimens		
1	71 (20.5)	39 (22.4)
2	106 (30.5)	56 (32.2)

Table 11. Summary of Demographic and Other Baseline Characteristics PALOMA-3 (Intent-to-Treat Population)

Characteristics	IBRANCE + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
3	98 (28.2)	35 (20.1)
>3	72 (20.7)	44 (25.3)
Prior lines of therapy in the metastatic setting:		
0	84 (24.2)	45 (25.9)
1	132 (38.0)	70 (40.2)
2	90 (25.9)	43 (24.7)
≥3	41 (11.8)	16 (9.2)
Previous chemotherapy regimen for primary diagnosis, n (%)		
No	95 (27.4)	37 (21.3)
Yes	252 (72.6)	137 (78.7)
Previous hormonal regimen for primary diagnosis, n (%)		
1	134 (38.6)	77 (44.3)
>1	213 (61.4)	97 (55.7)

Data source: Table 1023.511.4, Table 1023.511.6, Table 1023.511.7, Table 1023.511.8, and Table 1023.511.9.
ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; N=total number of patients in population; n=number of patients meeting prespecified criteria.
a. Based on randomization.
b. Postmenopausal status defined by at least 1 of the following criteria: 1) ≥60 years of age; 2) <60 years of age and cessation of regular menses for at least 12 consecutive months, with no alternative pathological or physiological cause, and serum estradiol and follicle stimulating hormone level within the laboratory's reference range for postmenopausal women; 3) documented bilateral oophorectomy; or 4) medically confirmed ovarian failure. Pre- or perimenopausal status defined as not meeting the criteria for being postmenopausal.

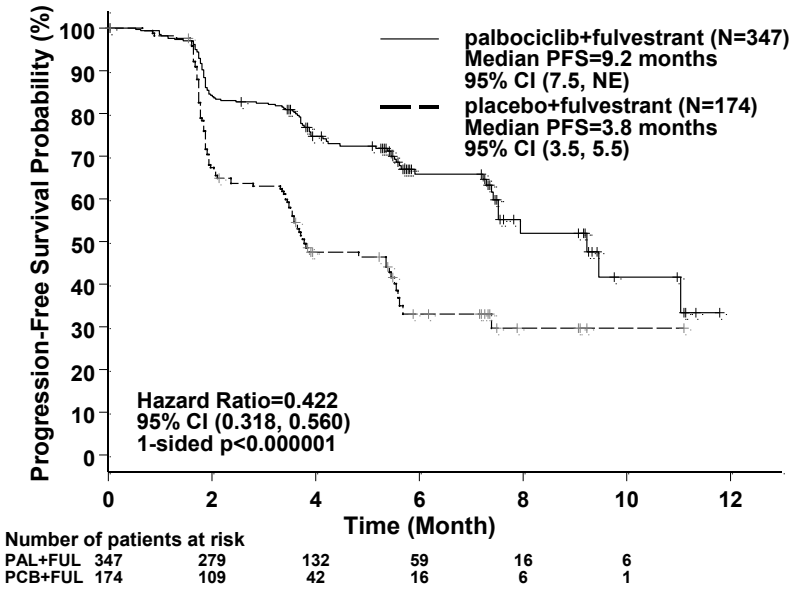
The primary endpoint of the study was investigator-assessed PFS, defined as the interval from randomization to the earlier of the first documentation of progressive disease or death from any cause, evaluated according to RECIST 1.1. Secondary endpoints included OS and objective response (OR). The primary analysis, performed at a median follow-up of 5.6 months, indicated that patients treated with IBRANCE plus fulvestrant had a statistically significant 57% reduction in the risk of progression compared to those treated with placebo plus fulvestrant. Efficacy results for PALOMA-3 are shown below in Table 12, and the Kaplan-Meier curve for PFS is shown in Figure 3.

Table 12 – Primary Efficacy Results – PALOMA-3 (Investigator Assessment, Intent-to-Treat Population)

	IBRANCE plus Fulvestrant (N=347)	Placebo plus Fulvestrant (N=174)
Progression-Free Survival		
Number of PFS Events (%)	102 (29.4%)	93 (53.4%)
Hazard ratio (95% CI) and p-value	0.422 (0.318, 0.560), p<0.000001	
Median PFS [months] (95% CI) at Interim Analysis	9.2 (7.5, NE)	3.8 (3.5, 5.5)

N=number of patients; CI=confidence interval; NE=not estimable; PFS = Progression-Free Survival;

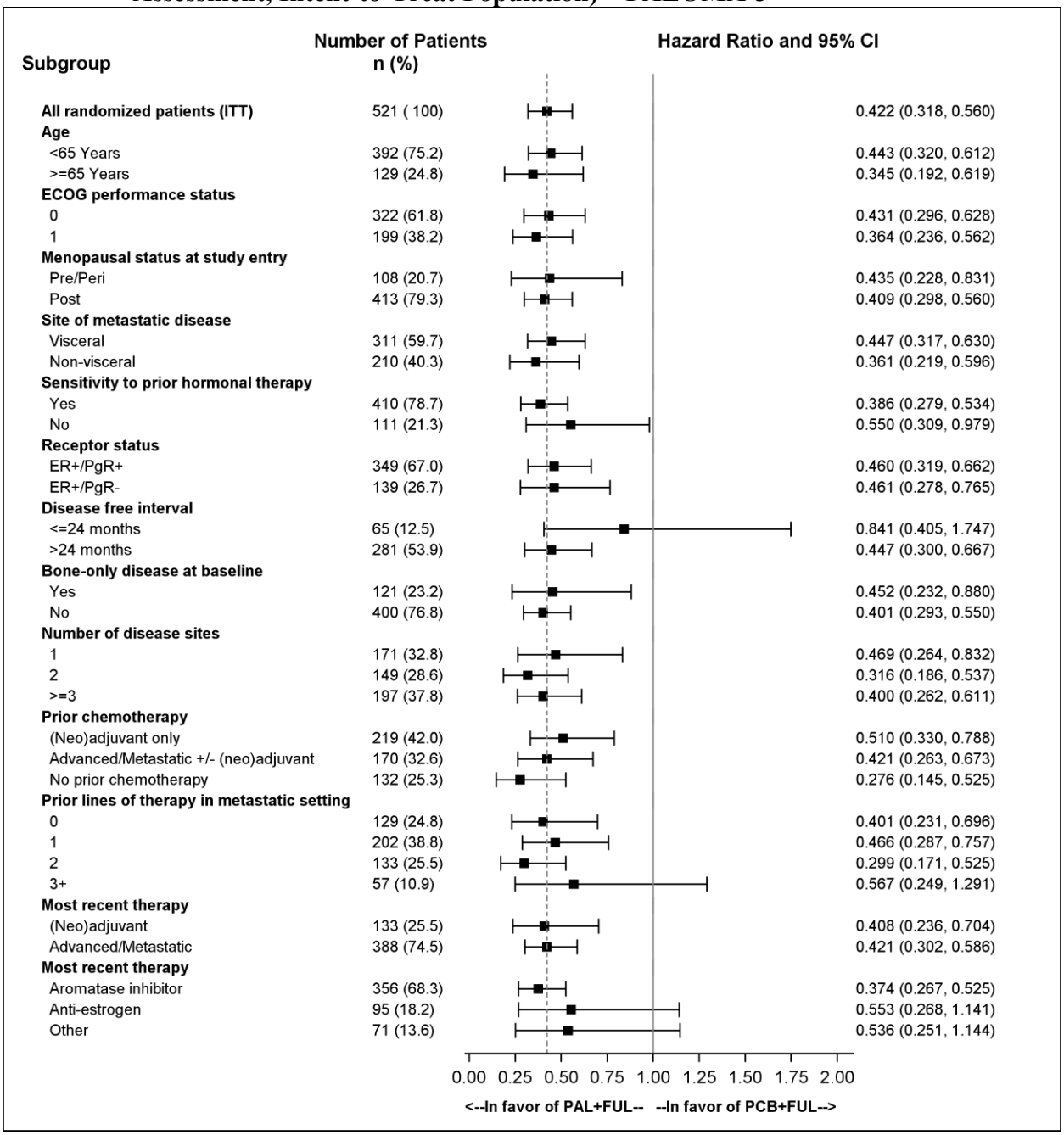
Figure 3. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3



Source: Section 14.2, Table 14.2.1.1.1 and Section 16.2, Table 16.2.6.2.3
Abbreviations: CI: confidence interval, FUL: fulvestrant, N: number of patients, PAL: palbociclib, PCB: placebo, PFS: progression-free survival, NE: not estimable

Consistent PFS results were observed across patient subgroups (see Figure 4).

Figure 4. Forest Plot of Subgroup Analyses of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3



Abbreviations: CI: confidence interval, CRF: case report form, ECOG: Eastern Cooperative Oncology Group, ER+: estrogen receptor positive, ITT: intent-to-treat, FUL: fulvestrant, n: number of patients, PAL: palbociclib, PCB: placebo, PgR+/-: progesterone receptor positive/negative. Note: The HR (95% CI) provided for all randomized patients (ITT) is based on the stratified analysis

An updated PFS analysis, performed at median duration of follow-up of 15.8 months for patients treated with IBRANCE plus fulvestrant, and 15.3 months for patients treated with placebo plus fulvestrant, was consistent with the primary analysis results, and indicated a 50% reduction in the risk of progression in favor of IBRANCE plus fulvestrant treatment over placebo plus fulvestrant (HR=0.497, 95% CI: 0.398, 0.620), with a median PFS of 11.2 months (95% CI: 9.5, 12.9) compared to 4.6 months (95% CI: 3.5, 5.6), respectively. At the time of this updated analysis, ORR for the ITT population with measurable disease was higher in the IBRANCE plus fulvestrant arm (27.3%; 95% CI: 22.1, 33.1) compared with the placebo plus fulvestrant arm (10.9%; 95% CI: 6.2, 17.3).

At the time of final analysis of PFS, overall survival (OS) data were not mature. No survival benefit has been demonstrated.

DETAILED PHARMACOLOGY

Pharmacodynamics

Palbociclib is a potent inhibitor of recombinant human CDK4 and CDK6 enzymes in biochemical assays with inhibition of CDK4/cyclinD_1, CDK4/cyclinD_3, and CDK6/cyclinD_2 at IC_{50} values of 11 nM (4.9 ng/mL), 9 nM (4.0 ng/mL), and 15 nM (6.7 ng/mL), respectively. Palbociclib inhibited the phosphorylation of retinoblastoma protein (Rb), a direct target of CDK4 and CDK6, at multiple sites including S780, S795, S807, and S811 with IC50 values ranging from 9 to 66 nM in ER positive breast cancer cells.

Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high efficacy against luminal ER-positive breast cancers. Mechanistic analyses revealed that the combination of palbociclib with anti-estrogen agents enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signaling and synergistic growth arrest. The enhanced growth arrest of the ER-positive breast cancer cell lines treated with palbociclib and anti-estrogen agents was accompanied by increased cell senescence resulting in a sustained cell cycle arrest following drug removal.

In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole enhanced inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.

In the presence or absence of an antiestrogen, palbociclib-treated bone marrow cells did not become senescent and resumed proliferation following palbociclib withdrawal, consistent with pharmacologic quiescence. In vitro breast cancer cells, however, became senescent following palbociclib or antiestrogen treatment, with additive effects observed in combination treatment, and remained arrested in the presence of antiestrogen treatment after the withdrawal of palbociclib.

Safety Pharmacology

Palbociclib inhibited currents (IC_{50} of 3.2 μM; 1432 ng/mL) in HEK293 cells stably expressing human ether-à-go-go related gene (hERG) potassium channels. Palbociclib caused a small but

statistically significant increase on action potential duration at 90% repolarization (APD_{90}) at 10 μM (4475 ng/mL) in a Purkinje assay assessment (8.2%), but had no effect at ≤1 μM (447.5 ng/mL).

QT and QTc interval prolongation were observed in telemetered dogs at unbound plasma concentrations (C_{max}) ≥ 67 ng/mL (approximately 4 times human clinical exposure based on C_{max}). Cardiovascular effects (decreased heart rate with a corresponding increase in RR interval, and a modest increase in systolic blood pressure) were also observed at unbound C_{max} ≥ 140 ng/mL (approximately 8 times human clinical exposure).

While palbociclib caused decreased activity in a rat neurofunctional assessment, there were no effects on any other measurement of the functional observational battery at up to 300 mg/kg (approximately 47 times human clinical exposure based on C_{max}).

In an anesthetized dog respiratory model, palbociclib caused significant effects on pulmonary parameters (increased minute volume and respiratory rate, and decreased compliance, peak expiratory flow, and tidal volume) at 5 mg/kg (approximately 50 times human clinical exposure based on C_{max}). Changes in pulmonary function noted at 1 mg/kg were not considered adverse (approximately 4 times human clinical exposure based on C_{max}).

TOXICOLOGY

Single- and Repeated-dose Toxicity

The nonclinical toxicology profile of palbociclib has been investigated in the rat and dog. Consistent with the intended pharmacologic effect of palbociclib (ie, cell cycle inhibition, CDK4/6 inhibition), the primary target organ findings included hematolymphopoietic and male reproductive organ effects following single and/or repeat dosing in rats up to 27 weeks and in dogs up to 39 weeks. Altered glucose metabolism accompanied by effects on the pancreas and secondary changes in the eye, teeth, kidney, and adipose tissue, and effects on bone were observed in rats only following repeated intermittent administration for ≥15 weeks.

Bone marrow effects were identified following single doses ≥30 mg/kg in the dog, with hypocellularity of the bone marrow that was reflected in peripheral hematology by decreases in all cell lineages. Following repeat-dose administration up to 27 weeks (rat) or 39 weeks (dog) in duration, the bone marrow effects were observed in rats and dogs, along with effects on lymphoid tissues (decreased cellularity) and male reproductive organs (seminiferous tubule degeneration, and secondary epididymal, prostate, and seminal vesicle effects) at ≥10 and 0.2 mg/kg/day, respectively (approximately 3- and 0.1 times human clinical exposure based on AUC, respectively). Altered glucose metabolism (hyperglycemia/glucosuria) was identified in rats in longer duration studies (≥15 weeks duration) and correlated with pancreatic islet cell vacuolation at ≥10 mg/kg/day (at human clinical exposures based on AUC). The pancreatic vacuolation was determined to reflect a loss of beta cells with corresponding decreases in insulin and C-peptide. The glucose dysregulation led to secondary changes in the eye (cataracts/lens degeneration), incisor teeth (ameloblast degeneration, pigmented macrophage infiltrates), kidney (tubule vacuolation), and adipose tissue (atrophy) at ≥10 mg/kg/day (at human clinical exposures based on AUC) following chronic (27 weeks) dosing in the rat. Altered glucose metabolism and

secondary changes noted in rats were not observed in dogs in repeat dosing studies up to 39 weeks in duration. An effect on bone (decreased trabeculae) was also observed in male rats at ≥10 mg/kg/day following chronic dosing (approximately 3-times human clinical exposure based on AUC). Partial to full recovery was shown for the hematolymphopoietic, male reproductive organ, teeth, and adipose tissue effects following a 4- or 12-week non-dosing period; however, reversibility was not established for the changes in glucose homeostasis, or the pancreas, eye, kidney, and bone.

Dose-limiting toxicity resulting in mortality occurred in rats (≥1000 mg/kg in a single dose study; 300 mg/kg/day [males] in a 2-week study; ≥200 mg/kg/day in a 3-week study; 100 mg/kg/day in a 15- [single TK animal] and 27-week study) and dogs (≥30 mg/kg in a dose-escalation study; 10 mg/kg/day in a 2-week study).

Carcinogenicity
Carcinogenicity studies have not been conducted with palbociclib.

Genotoxicity
Palbociclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the in vitro human lymphocyte chromosome aberration assay. Palbociclib induced micronuclei via an aneugenic mechanism in Chinese hamster ovary cells in vitro and in the bone marrow of male rats at doses ≥100 mg/kg/day. The no observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

Reproductive and Developmental Toxicity
In a fertility study in female rats, palbociclib did not affect mating or fertility at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC) and no adverse effects were observed in the female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 5 and 3 times human clinical exposure based on AUC, respectively).

Palbociclib-related male reproductive organ findings in repeat-dose toxicity studies consisted of testicular degeneration and secondary effects on the epididymis (ductal atrophy, hypospermia, intratubular cellular debris), prostate (atrophy, decreased content), and seminal vesicle (decreased secretion). These effects were observed in rats and/or dogs at ≥30 and 0.2 mg/kg/day, respectively (approximately 7 and 0.1 times human clinical exposure based on AUC, respectively). Partial reversibility of male reproductive organ effects was observed in rats and dogs following a 4- and 12-week non-dosing period, respectively. In the fertility and early embryotic development study in male rats, at projected exposure levels (AUC) of 13 times the exposure in humans at the recommended dose, palbociclib caused no effects on mating, but the females that mated with males had lower pregnancy rates (88.9%) compared to the females that successfully mated with males from the lower dose and control groups (100%).

Palbociclib was shown to be fetotoxic in pregnant rats or rabbits. Palbociclib administered to pregnant rats at doses of 30, 100, or 300 mg/kg/day during the period of organogenesis caused reduced fetal body weights at a maternally toxic dose of 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC). An increased incidence of cervical ribs was observed at doses ≥100 mg/kg/day (≥1 times the human clinical exposures based on AUC). Palbociclib

administered to pregnant rabbits at doses of 2, 10, or 20 mg/kg/day during the period of organogenesis was associated with small forepaw phalanges at a maternally toxic dose of 20 mg/kg/day (approximately 4 times human clinical exposure based on AUC). Palbociclib-related changes in skeletal ossification (increase in the average number of rib pairs) occurred at doses ≥ 10 mg/kg/day (≥ 2 times human clinical exposure based on AUC). Reduced fetal body weights in the rat and small forepaw phalanges in the rabbit were considered adverse at 300 and 20 mg/kg/day, respectively (approximately 3- and 4-times human clinical exposure based on AUC, respectively).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

IBRANCE is used:
-along with the medicine letrozole to treat breast cancer that has spread to other parts of the body. It is used in postmenopausal women to treat certain types of breast cancers that are estrogen receptor positive.

It has been approved *with conditions*. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

It has also been approved without conditions for use along with the medicine fulvestrant in women to treat breast cancer that has spread to other parts of the body. It is used to treat certain types of breast cancer that are hormone receptor positive and have come back or have not responded to previous hormonal treatment.

What is a Notice of Compliance with Conditions (NOC/c)?
Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

[Pr]IBRANCE™
Palbociclib Capsules

Read this carefully before you start taking **IBRANCE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IBRANCE**.

Your breast cancer will be treated with IBRANCE in combination with letrozole or fulvestrant. Read the letrozole or fulvestrant Patient Medication Information leaflet carefully as well as this one.

Serious Warnings and Precautions

Take IBRANCE under the care of a doctor who knows how to use anti-cancer drugs.

- IBRANCE may cause the number of white blood cells in your blood to be abnormally low.

What is IBRANCE used for?

IBRANCE is a prescription medicine used:

- along with the medicine letrozole to treat breast cancer that has spread to other parts of the body. It is used in postmenopausal women to treat certain types of breast cancers that are estrogen receptor positive.
- along with the medicine fulvestrant in women to treat breast cancer that has spread to other parts of the body. It is used to treat certain types of breast cancer that are hormone receptor positive and have come back or have not responded to previous hormonal treatment. Women who have not gone through menopause must also take a medicine to stop their ovaries from making estrogen.

How does IBRANCE work?

Palbociclib belongs to a family of medications called kinase inhibitors. These medications work by stopping cancer cells from dividing and growing. When given together with letrozole or fulvestrant, IBRANCE may slow down the growth and spread of breast cancer cells.

What are the ingredients in IBRANCE?

Medicinal ingredients: Palbociclib

Non-medicinal ingredients:

ammonium hydroxide, colloidal silicon dioxide, gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, red iron oxide, shellac, simethicone, sodium starch glycolate, titanium dioxide, and yellow iron oxide.

IBRANCE comes in the following dosage forms:

Capsules: 75 mg, 100 mg and 125 mg

Do not use IBRANCE if:
You are allergic to palbociclib or any of the other ingredients of IBRANCE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IBRANCE. Talk about any health conditions or problems you may have, including if you:
- Have fever, chills, or any other signs or symptoms of infection
- Have heart problems, including a condition called long QT syndrome.
- Have liver or kidney problems.
- Have any other medical conditions.
- Are pregnant, or plan to become pregnant. IBRANCE may harm your unborn baby.
- Are a woman who is able to become pregnant. IBRANCE is recommended for use only in women who are postmenopausal and thus unable to become pregnant. If you are able to become pregnant and are taking IBRANCE, you should use birth control during treatment and for at least 21 days after stopping IBRANCE. Talk to your doctor about the birth control methods that may be right for you. If you become pregnant, tell your doctor right away.
- Are breastfeeding or plan to breastfeed. It is not known if IBRANCE passes into breast milk. You and your doctor should decide if you will take IBRANCE or breastfeed. You should not do both.

Other warnings you should know about:

IBRANCE may cause:
- **Serious or life-threatening infections**. Your doctor will decide when to perform blood tests and will interpret the results. Tell your doctor right away if you have fever, chills, or any other signs or symptoms of infection.
- **Pulmonary embolism** (a blockage in the lungs).
- **Neutropenia and Leukopenia** (low white blood cells)
- **Anemia** (low red blood cells)

IBRANCE should not be used in children and adolescents under 18 years of age.

Driving and using machines: Fatigue and dizziness can occur with IBRANCE. Be careful when driving or operating machinery while you are taking IBRANCE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

The following may interact with IBRANCE:
- Medicines for infections (antibiotics), such as clarithromycin, nafcillin, rifampin and telithromycin
- Medicines for fungal infections, such as ketoconazole, itraconazole, posaconazole and voriconazole

- Some medicines for high blood pressure, such as bosentan
- HIV medicines, such as saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, efavirenz and etravirine
- Antiviral medicines, such as telaprevir
- Antidepressant medicines, such as nefazodone
- Medicines to treat epilepsy, such as carbamazepine and phenytoin
- Medicines to treat certain types of sleep disorders, such as modafinil
- St. John's wort
- Do not drink grapefruit juice or eat grapefruit, or products containing grapefruit extracts, star fruit, pomegranate, Seville oranges or other similar fruits. They may change the amount of IBRANCE in your body.

Other drugs not listed here may also interact

How to take IBRANCE:

- Take IBRANCE exactly as your doctor tells you.
- Swallow IBRANCE capsules whole. Do NOT crush, dissolve or open the capsules.
- You should take IBRANCE with food once daily for 21 days. This is followed by 7 days off (3 weeks on, 1 week off) for a 28 day cycle.
- Take IBRANCE at approximately the same time each day.
- If you vomit after taking a dose of IBRANCE, do not take an extra dose. Take your next dose at your regular time.

Recommended starting dosage strength:
125 mg

Usual Adult dose:
1 capsule once a day with food for 21 days.

Overdose:

If you think you have taken too much IBRANCE contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a day's dose, do not take an extra dose the next day. Take your next dose at your regular time.

What are possible side effects from using IBRANCE?

These are not all the possible side effects you may feel when taking IBRANCE. If you experience any of these side effects or side effects not listed here, contact your healthcare professional. Please also see the Serious Warnings and Precautions Box.

Side effects may include:

- Decrease in the number of white blood cell, red blood cell and platelet counts in the bloodstream
- Shortness of breath
- Tiredness or weakness
- Cough
- Mouth sores
- Unusual hair thinning or loss
- Nausea, vomiting
- Bruising
- Loss of appetite
- Tingling or abnormal feeling (especially in arms and legs)
- Nose bleed
- Headache
- Diarrhea
- Constipation
- Rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Neutropenia and Leukopenia: infection, fever		√	
Infections:, fever, chills, dizziness, weakness, shortness of breath		√	
Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
COMMON			
Increased tendency to bruise or bleed		√	
Diarrhea	√		
Fever		√	
Pulmonary embolism: sudden shortness of breath, chest pain and cough.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store IBRANCE at room temperature between 20°C to 25°C; excursions permitted between 15°C to 30°C.
Keep out of reach and sight of children.

If you want more information about IBRANCE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada Inc.

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