HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IBRANCE safely and effectively. See full prescribing information for IBRANCE.

IBRANCE® (palbociclib) capsules, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

IBRANCE is a kinase inhibitor 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. (1) This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (14)

DOSAGE AND ADMINISTRATION

IBRANCE capsules are taken orally with food in combination with letrozole. (2)

- Recommended starting dose: 125 mg once daily taken with food for 21 days followed by 7 days off treatment. (2.1)
- Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 125 mg, 100 mg, and 75 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hematologic: Neutropenia may occur. Monitor complete blood count prior to start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated. (5.1)
- Infections: Monitor for signs and symptoms and withhold dosing as appropriate. (5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10%) were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- CYP3A Inhibitors: Avoid concurrent use of IBRANCE with strong CYP3A inhibitors. If the strong inhibitor cannot be avoided, reduce the IBRANCE dose. (2.2, 7.1)
- CYP3A Inducers: Avoid concurrent use of IBRANCE with strong and moderate CYP3A inducers. (7.2)
- CYP3A Substrates: The dose of sensitive CYP3A4 substrates with narrow therapeutic indices may need to be reduced when given concurrently with IBRANCE. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IBRANCE is 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.

This indication is approved under accelerated approval based on progression-free survival (PFS) *[see Clinical*

Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended dose of IBRANCE 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 *[see Clinical Pharmacology (12.3)]* in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle. Patients should be encouraged to take their dose at approximately the same time each day.

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.

2.2 Dose Modification

Dose modification of IBRANCE is recommended based on individual safety and tolerability *[see Warnings and Precautions (5)]*.

Management of some adverse reactions *[see Warnings and Precautions (5)]* may require temporary dose interruptions/delays and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2 and 3 *[see Warnings and Precautions (5), Adverse Reactions (6) and Clinical Studies (14)]*.

Table 1. Recommended Dose Modification for Adverse Reactions

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 the treatment.

Table 2. Dose Modification and Management* – Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3†	No dose adjustment is required. Consider repeating complete blood count monitoring one week later. Withhold initiation of next cycle until recovery to Grade ≤2.
Grade 3 ANC (<1000 to 500/mm^3) + Fever ≥38.5ºC and/or infection	Withhold IBRANCE and initiation of next cycle until recovery to Grade ≤2 (≥1000/mm^3). Resume at next lower dose.
Grade 4†	Withhold IBRANCE and initiation of next cycle until recovery to Grade ≤2. Resume at next lower dose.

Grading according to CTCAE Version 4.0.

ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events.

* Monitor complete blood count prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated.

† Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Table 3. 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 lower dose.

Grading according to CTCAE Version 4.0.
CTCAE=Common Terminology Criteria for Adverse Events.

See manufacturer's prescribing information for the coadministered product, letrozole, dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

Dose Modifications for Use With Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be coadministered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

125 mg capsules: opaque hard gelatin capsules, size 0, with caramel cap and body, printed with white ink "Pfizer" on the cap, "PBC 125" on the body.

100 mg capsules: 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.

75 mg capsules: 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.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Decreased neutrophil counts have been observed in clinical trials with IBRANCE. Grade 3 (57%) or 4 (5%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole in the randomized

clinical trial (Study 1). Median time to first episode of any grade neutropenia per laboratory data was 15 days (13–117 days). Median duration of Grade ≥3 neutropenia was 7 days *[see Adverse Reactions (6.1)]*.

Febrile neutropenia events have been reported in the IBRANCE clinical program, although no cases of febrile neutropenia have been observed in Study 1. Monitor complete blood count prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated. 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 (2.2)]*.

5.2 Infections

Infections have been reported at a higher rate in patients treated with IBRANCE plus letrozole compared to patients treated with letrozole alone in Study 1. Grade 3 or 4 infections occurred in 5% of patients treated with IBRANCE plus letrozole whereas no patients treated with letrozole alone experienced a Grade 3 or 4 infection. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

5.3 Pulmonary Embolism

Pulmonary embolism has been reported at a higher rate in patients treated with IBRANCE plus letrozole (5%) compared with no cases in patients treated with letrozole alone in Study 1. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

5.4 Embryo-Fetal Toxicity

Based on findings in animals and mechanism of action, IBRANCE can cause fetal harm. IBRANCE caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were greater than or equal to 4 times the human clinical exposure based on area under the curve (AUC). Advise females of reproductive potential to use effective contraception during therapy with IBRANCE and for at least two weeks after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following topics are described below and elsewhere in the labeling:

- Neutropenia *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Pulmonary Embolism *[see Warnings and Precautions (5.3)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus letrozole alone was evaluated in Study 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 treatment in Study 1. The median duration of treatment for palbociclib was 13.8 months while the median duration of treatment for letrozole on the letrozole-alone arm was 7.6 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation due to an adverse reaction occurred in 7 of 83 (8%) patients receiving IBRANCE plus letrozole and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%).

The most common adverse reactions (≥10%) 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 reactions in patients receiving IBRANCE plus letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%).

An increase incidence of infections events was observed in the palbociclib plus letrozole arm (55%) compared to the letrozole alone arm (34%). Febrile neutropenia events have been reported in the IBRANCE clinical program, although no cases were observed in Study 1. Grade ≥3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia *[see Dosage and Administration (2.2)]*.

Adverse drug reactions (≥10%) reported in patients who received IBRANCE plus letrozole or letrozole alone in Study 1 are listed in Table 4.

Table 4. Adverse Reactions[*] (≥10%) in Study 1

System Organ Class Adverse 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[†]	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[‡]	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis[§]	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

Grading according to CTCAE Version 3.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of subjects; N/A=not applicable; URI=Upper respiratory infection.

[*] Adverse Reaction rates reported in the table include all reported events regardless of causality.

[†] URI includes: Influenza, Influenza like illness, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper

respiratory tract infection.

‡ Peripheral neuropathy includes: Neuropathy peripheral, Peripheral sensory neuropathy.

§ Stomatitis includes: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

¶ Grade 1 events - 21%; Grade 2 events - 1%.

Grade 1 events - 3%.

Table 5. Laboratory Abnormalities for Patients in Study 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 patients.

7 DRUG INTERACTIONS

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

7.1 Agents That May Increase Palbociclib Plasma Concentrations

Effect of CYP3A Inhibitors

Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole). Avoid grapefruit or grapefruit juice during IBRANCE treatment. If coadministration of IBRANCE with a strong CYP3A inhibitor cannot be avoided, reduce the dose of IBRANCE *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

7.2 Agents That May Decrease Palbociclib Plasma Concentrations

Effect of CYP3A Inducers

Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine and St John's Wort) *[see Clinical Pharmacology (12.3)]*.

Coadministration of moderate CYP3A inducers may also decrease the plasma exposure of IBRANCE. Avoid concomitant use of moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) *[see Clinical Pharmacology (12.3)]*.

7.3 Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, 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 *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal studies, palbociclib was teratogenic and fetotoxic at maternal exposures that were ≥4 times the human clinical exposure based on AUC at the recommended human dose. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2–4% and of miscarriage is 15–20% of clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, palbociclib was administered orally for 15 days before mating through to Day 7 of pregnancy, which did not cause embryo toxicity at doses up to 300 mg/kg/day with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 300 mg/kg/day and 20 mg/kg/day palbociclib, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses ≥100 mg/kg/day in rats, there was an increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). At the maternally toxic dose of 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small phalanges in the forelimb. At 300 mg/kg/day in rats and 20 mg/kg/day in rabbits, the maternal systemic exposures were approximately 4 and 9 times the human exposure (AUC) at the recommended dose.

CDK4/6 double knockout mice have been reported to die in late stages of fetal development (gestation Day 14.5 until birth) due to severe anemia. However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

8.2 Lactation

Risk Summary

There are no data on the presence of palbociclib in human milk, the effects of IBRANCE on the breastfed child, or the effects of IBRANCE on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IBRANCE, advise a nursing woman to discontinue breastfeeding during treatment with IBRANCE.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE *[see Use in Specific Populations*

(8.1)].

Infertility

Males

Based on findings in animals, male fertility may be compromised by treatment with IBRANCE *[see Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of IBRANCE in pediatric patients have not been studied.

8.5 Geriatric Use

Of 84 patients who received IBRANCE in Study 1, 37 patients (44%) were ≥65 years of age and 8 patients (10%) were ≥75 years of age. No overall differences in safety or effectiveness of IBRANCE were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Based on a population pharmacokinetic analysis that included 183 patients, 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) *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

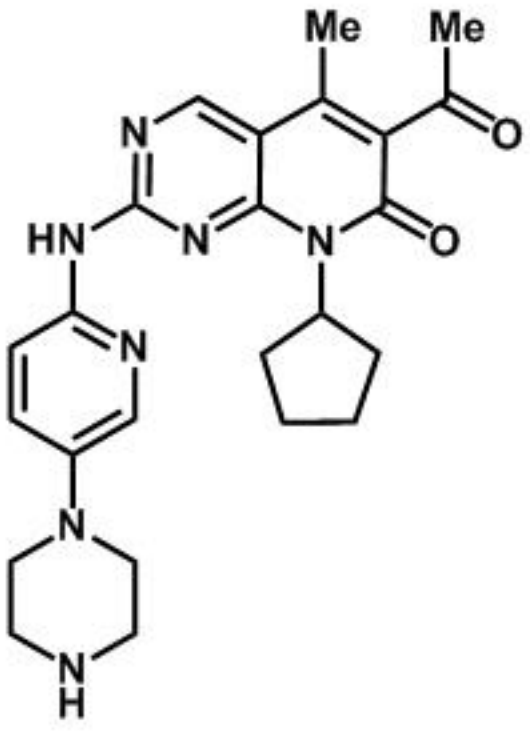
Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

11 DESCRIPTION

IBRANCE capsules for oral administration contain 125 mg, 100 mg, or 75 mg of palbociclib, a kinase inhibitor. The molecular formula for palbociclib is $C_{24}H_{29}N_7O_2$. The molecular weight is 447.54 daltons. The chemical name is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one, and its structural formula is:



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.

Inactive ingredients: 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and antiestrogens leads to decreased retinoblastoma protein (Rb) phosphorylation resulting in reduced E2F expression and signaling and increased growth arrest compared to treatment with each drug alone. In vitro treatment of ER-positive breast cancer cell lines with the combination of palbociclib and antiestrogens leads to increased cell senescence, which was sustained for up to 6 days following drug removal. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of palbociclib on the QTc interval was evaluated in 184 patients with advanced cancer. No large change (i.e., >20 ms) in the QTc interval was detected 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).

12.3 Pharmacokinetics

The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

Absorption

The mean C_{max} of palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration, T_{max}) following oral administration. 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: Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the intersubject variability of palbociclib exposure, which supports administration of IBRANCE with food. Compared to IBRANCE given under overnight fasted conditions, the population average AUC_{inf} and C_{max} of palbociclib increased by 21% and 38%, respectively, when given with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively), by 12% and 27%, respectively, when given with low-fat, low-calorie food (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate and fat, respectively), and by 13% and 24%, respectively, when moderate-fat, standard calorie food (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate and fat, respectively) was given one hour before and two hours after IBRANCE dosing.

Distribution

Binding of palbociclib to human plasma proteins in vitro was approximately 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 (26% CV).

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 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%). The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 26% of the administered dose. In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant SULT enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/hr (29% CV), and the mean (± standard deviation) plasma elimination half-life was 29 (±5) 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.

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), gender had no effect on the

exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Pediatric Population

Pharmacokinetics of IBRANCE have not been evaluated in patients <18 years of age.

Drug Interactions

In vitro data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. 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.

CYP3A Inhibitors: Data from a drug interaction trial in healthy subjects (N=12) indicate that coadministration of multiple 200 mg daily doses of itraconazole with a single 125 mg IBRANCE dose increased palbociclib AUC_{inf} and the C_{max} by approximately 87% and 34%, respectively, relative to a single 125 mg IBRANCE dose given alone.

CYP3A Inducers: Data from a drug interaction trial in healthy subjects (N=14) indicate that coadministration of multiple 600 mg daily doses of rifampin with a single 125 mg IBRANCE dose decreased palbociclib AUC_{inf} and the C_{max} by 85% and 70%, respectively, relative to a single 125 mg IBRANCE dose given alone.

CYP3A Substrates: Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In a drug interaction trial in healthy subjects (N=26), 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.

Gastric pH Elevating Medications: In a drug interaction trial in healthy subjects, coadministration of a single 125 mg dose of IBRANCE with multiple doses of the proton pump inhibitors (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. 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. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure. In another healthy subject study, coadministration of a single 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 to a single dose of IBRANCE administered alone.

Letrozole: Data from a drug interaction trial in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the two drugs were coadministered.

Effect of Palbociclib on 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)2 and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations.

Effect of Transporters on Palbociclib: Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with palbociclib.

Palbociclib was clastogenic in an in vitro micronucleus assay in Chinese Hamster Ovary cells and in vivo in the

bone marrow of male rats that received doses ≥100 mg/kg/day for three weeks. Clastogenicity occurred via an aneugenic mechanism. Palbociclib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the in vitro human lymphocyte chromosome aberration assay.

In a fertility study in female rats, palbociclib did not affect mating or fertility at any dose up to 300 mg/kg/day (approximately 4 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 6 times and similar to human exposure (AUC), at the recommended dose, respectively). Male fertility studies with palbociclib have not been conducted; however, in repeat-dose toxicity studies, testicular degeneration was observed in rats and dogs at 30 and 0.2 mg/kg/day, respectively (approximately 11 and 0.1 times human exposure (AUC), at the recommended dose, respectively), which was partially reversible in the rat and dog following a 12-week non-dosing period.

13.2 Animal Toxicology and/or Pharmacology

Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), teeth (degeneration/necrosis of ameloblasts in actively growing teeth), kidney (tubule vacuolation, chronic progressive nephropathy), and adipose tissue (atrophy) were identified in the 27-week repeat-dose toxicology study in rats and were most prevalent in males at doses ≥30 mg/kg/day (approximately 11 times the human exposure (AUC) at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present in the 15-week repeat-dose toxicology study in rats, but with lower incidence and severity. The rats used in these studies were approximately 7 weeks old at the beginning of the studies. Altered glucose metabolism or associated changes in pancreas, eye, teeth, kidney, and adipose tissue were not identified in dogs in repeat-dose toxicology studies up to 39 weeks duration.

14 CLINICAL STUDIES

Study 1 was a randomized, open-label, multicenter study 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. A total of 165 patients were randomized in Study 1. Randomization was 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). IBRANCE was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Patients received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal.

Patients enrolled in this study had a median age of 63 years (range 38 to 89). The majority of patients were Caucasian (90%) and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Forty-three percent of patients had received chemotherapy and 33% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Forty-nine percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (98%) had metastatic disease. Nineteen percent of patients had bone only disease and 48% of patients had visceral disease.

The major efficacy outcome measure of the study was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST). Major efficacy results from Study 1 are summarized in Table 6 and Figure 1. Consistent results were observed across patient subgroups of, disease-free interval, disease site and prior therapy. The treatment effect of the combination on PFS was also supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.621 (95% CI: 0.378, 1.019). Overall response rate in patients with measurable disease as assessed by the investigator was higher in the IBRANCE plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%). At the time of the final

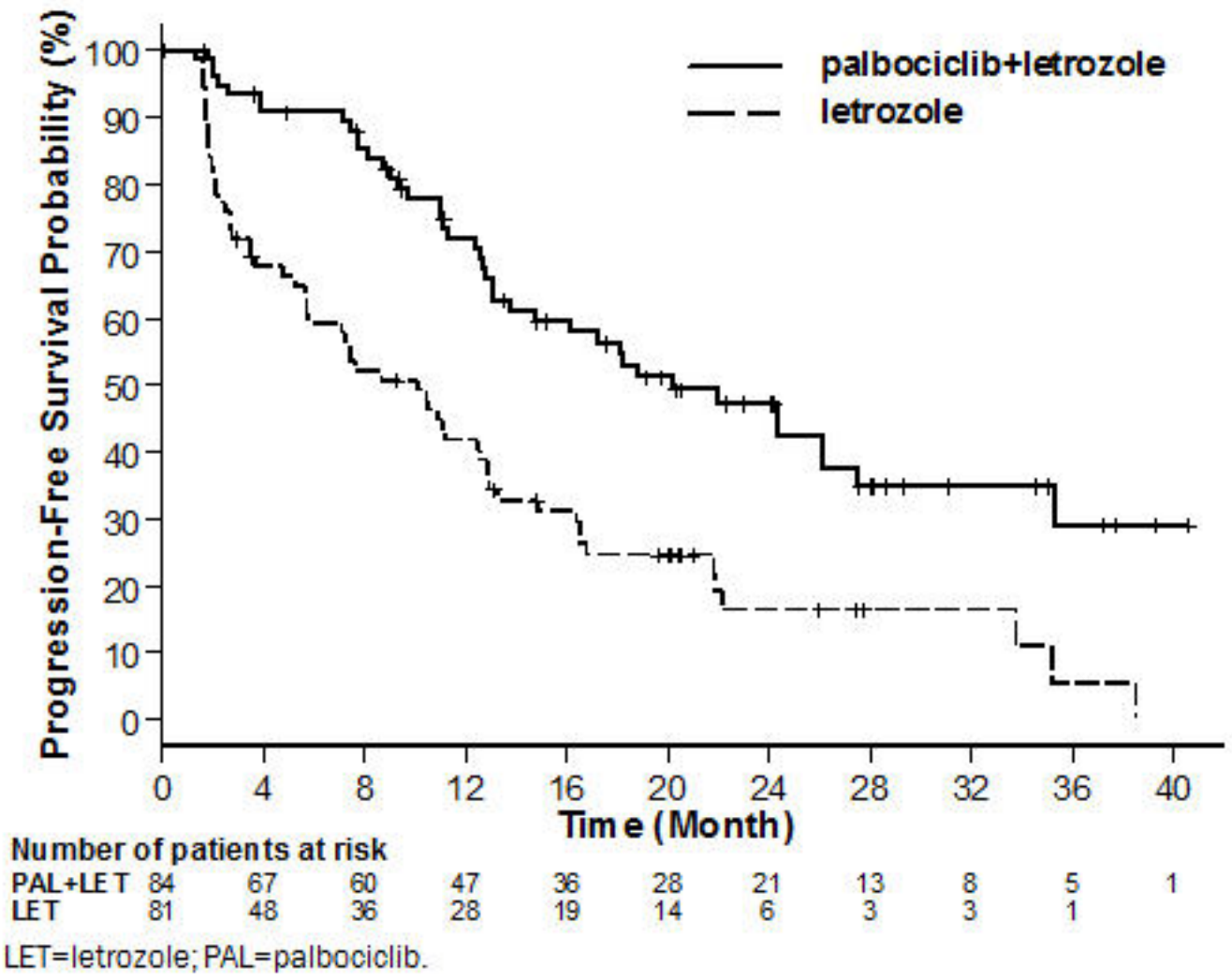
analysis of PFS, overall survival (OS) data was not mature with 37% of events.

Table 6. Efficacy Results – Study 1 (Investigator Assessment, Intent-to-Treat Population)

	IBRANCE + Letrozole (N=84)	Letrozole (N=81)
Progression-Free Survival (PFS)		
Number of PFS Events (%)	41 (48.8%)	59 (72.8%)
Hazard ratio (95% CI)	0.488 (0.319, 0.748)	
Median PFS [months] (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)

CI=confidence interval; N=number of patients.

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



LET=letrozole; PAL=palbociclib.

16 HOW SUPPLIED/STORAGE AND HANDLING

IBRANCE is supplied in the following strengths and package configurations:

IBRANCE Capsules

Package Configuration	Capsule Strength (mg)	NDC	Capsule Description
Bottles of 21 capsules	125	NDC 0069-0189-21	opaque, hard gelatin capsules, size 0, with caramel cap and body, printed with white ink "Pfizer" on the cap, "PBC 125" on the body
			opaque, hard gelatin capsules, size 1, with

Bottles of 21 capsules	100	NDC 0069-0188-21	caramel cap and light orange body, printed with white ink "Pfizer" on the cap, "PBC 100" on the body
Bottles of 21 capsules	75	NDC 0069-0187-21	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

Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F).

17 PATIENT COUNSELING INFORMATION

See *FDA-approved patient labeling (Patient Information)*.

- Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness or any increased tendency to bleed and/or to bruise *[see Warnings and Precautions (5.2)]*.
- Advise patients to immediately report any signs or symptoms of pulmonary embolism, such as shortness of breath, chest pain, tachypnea, and tachycardia *[see Warnings and Precautions (5.3)]*.
- Advise patients to take IBRANCE with food and swallow IBRANCE capsules whole.
- IBRANCE may interact with grapefruit. Patients should not consume grapefruit products while on treatment with IBRANCE.
- Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.
- 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.
- Advise females of reproductive potential to use effective contraception during IBRANCE therapy and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with IBRANCE *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1 and 8.3)]*.

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com.

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LAB-0723-1.0

PATIENT INFORMATION
IBRANCE® (EYE-brans)
(palbociclib)
capsules

What is the most important information I should know about IBRANCE?

IBRANCE may cause serious side effects, including:

Low white blood cell counts (neutropenia). Low white blood cell counts are common when taking

IBRANCE. Your healthcare provider should check your white blood cell counts before and during treatment.

If you develop low white blood cell counts during treatment with IBRANCE, your healthcare provider may stop your treatment, decrease your dose, or may tell you to wait to begin your treatment cycles.

Infections. IBRANCE may cause serious or life-threatening infections. Tell your healthcare provider right away if you develop any signs and symptoms of an infection such as fever or chills.

Blood clots in the arteries of your lungs (pulmonary embolism or PE). IBRANCE may cause serious or life-threatening blood clots in the arteries of your lungs. Tell your healthcare provider right away if you have any of the following signs and symptoms of a PE:

- shortness of breath
- sudden, sharp chest pain that may become worse with deep breathing
- rapid heart rate
- rapid breathing

See "What are the possible side effects of IBRANCE?" for more information about side effects.

What is IBRANCE?

IBRANCE is a prescription medicine that is used along with the medicine letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as the first hormone-based therapy for their metastatic disease.

It is not known if IBRANCE is safe and effective in children.

What should I tell my healthcare provider before taking IBRANCE?

Before you take IBRANCE, tell your healthcare provider if you:

- have fever, chills, or any other signs or symptoms of infection.
- have liver or kidney problems.
- have any other medical conditions.
- are pregnant, or plan to become pregnant. IBRANCE can harm your unborn baby.
  - Females who are able to become pregnant and who take IBRANCE should use effective birth control during treatment and for at least 2 weeks after stopping IBRANCE.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if IBRANCE passes into your breast milk. You and your healthcare provider should decide if you will take IBRANCE or breastfeed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. IBRANCE and other medicines may affect each other causing side effects.

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

How should I take IBRANCE?

- Take IBRANCE exactly as your healthcare provider tells you.
- Take IBRANCE with food.
- Swallow IBRANCE capsules whole. Do not chew, crush or open IBRANCE capsules before swallowing

them.

- Do not take any IBRANCE capsules that are broken, cracked, or that look damaged.
- Avoid grapefruit and grapefruit products during treatment with IBRANCE. Grapefruit may increase the amount of IBRANCE in your blood.
- Do not change your dose or stop taking IBRANCE unless your healthcare provider tells you.
- If you miss a dose of IBRANCE or vomit after taking a dose of IBRANCE, do not take another dose on that day. Take your next dose at your regular time.
- If you take too much IBRANCE, call your healthcare provider right away or go to the nearest hospital emergency room.

What are the possible side effects of IBRANCE?

IBRANCE may cause serious side effects. See "What is the most important information I should know about IBRANCE?"

Low red blood cell counts and low platelet counts are common with IBRANCE. Call your healthcare provider right away if you develop any of these symptoms during treatment:

- dizziness
- shortness of breath
- weakness
- bleeding or bruising more easily
- nosebleeds

Other common side effects of IBRANCE include:

- tiredness
- upper respiratory tract infection (see **"What is the most important information I should know about IBRANCE?"**)
- nausea
- numbness or tingling in your arms, hands, legs, and feet
- sore mouth
- unusual hair thinning or hair loss
- diarrhea
- decreased appetite
- vomiting
- weakness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of IBRANCE. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Pfizer, Inc. at 1-800-438-1985.

How should I store IBRANCE?

- Store IBRANCE at 68 °F to 77 °F (20 °C to 25 °C).

Keep IBRANCE and all medicines out of the reach of children.

General information about the safe and effective use of IBRANCE

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IBRANCE for a condition for which it was not prescribed. Do not give IBRANCE to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for more information about IBRANCE that is written for health professionals.

For more information, go to www.IBRANCE.com or call 1-800-438-1985.

What are the ingredients in IBRANCE?

Active ingredient: palbociclib

Inactive ingredients: Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells.

Light orange, light orange/caramel and caramel opaque capsule shells contain: gelatin, red iron oxide, yellow iron oxide, and titanium dioxide.

Printing ink contains: shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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