IBRANCE- palbociclib tablet, film coated
U.S. Pharmaceuticals

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) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1)	4/2025
Dosage and Administration (2.1, 2.2)	4/2025

INDICATIONS AND USAGE

IBRANCE is a kinase inhibitor indicated:

- for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:
  - an aromatase inhibitor as initial endocrine-based therapy (1); or
  - fulvestrant in patients with disease progression following endocrine therapy. (1)
- in combination with inavolisib and fulvestrant for the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. (1)

DOSAGE AND ADMINISTRATION

IBRANCE tablets are taken orally with or without food in combination with an aromatase inhibitor, fulvestrant, or inavolisib and fulvestrant. (2)

- Recommended starting dose: 125 mg once daily taken with or without food for 21 days followed by 7 days off treatment. (2.1)
- Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 125 mg, 100 mg, and 75 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Neutropenia: Monitor complete blood count prior to start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. (2.2, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Severe and fatal cases of ILD/pneumonitis have been reported. Monitor for pulmonary symptoms of ILD/pneumonitis. Interrupt IBRANCE immediately in patients with suspected ILD/pneumonitis. Permanently discontinue IBRANCE if severe ILD/pneumonitis occurs. (5.2)
- Embryo-Fetal Toxicity: IBRANCE can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20%) in combination with either letrozole or fulvestrant, including laboratory abnormalities, were white blood cell count decreased, neutrophils decreased, blood creatinine increased, hemoglobin decreased, platelets decreased, infections, aspartate aminotransferase increased, alanine aminotransferase increased, fatigue, nausea, stomatitis, diarrhea, and alopecia. (6.1)

The most common adverse reactions (incidence ≥20%) in combination with inavolisib and fulvestrant, including laboratory abnormalities, were neutrophils decreased, hemoglobin decreased, fasting glucose increased, platelets decreased, lymphocytes decreased, stomatitis, diarrhea, calcium decreased, fatigue, potassium decreased, creatinine increased, alanine aminotransferase (ALT) increased, nausea, sodium decreased, magnesium decreased, rash, decreased appetite, COVID-19 infection, and headache. (6.1)

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 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)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

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

Revised: 9/2025

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 for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant in patients with disease progression following endocrine therapy.

IBRANCE is indicated in combination with inavolisib and fulvestrant for the treatment of adult patients with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

The recommended dose of IBRANCE is a 125 mg tablet taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE tablet may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Administer the recommended dose of an aromatase inhibitor when given with IBRANCE. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

When given with IBRANCE, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant.

Refer to the Full Prescribing Information for inavolisib and fulvestrant for dosing information.

Advise patients to take their dose of IBRANCE at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE tablets should be

swallowed whole (do not chew, crush, or split them prior to swallowing). Tablets should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination IBRANCE plus an aromatase inhibitor or fulvestrant therapy or IBRANCE plus inavolisib and fulvestrant should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards.

For men treated with combination IBRANCE plus aromatase inhibitor or IBRANCE plus inavolisib and fulvestrant therapy, consider treatment with an LHRH agonist according to current clinical practice standards.

2.2 Dose Modification

The recommended dose modifications for adverse reactions are listed in Tables 1, 2, and 3.

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.

Table 2. Dose Modification and Management – Hematologic Toxicities*

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle 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 15 of first 2 cycles: If Grade 3 on Day 15, continue IBRANCE at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3

	neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia† with fever ≥38.5 °C and/or infection	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.
Grade 4	At any time: 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.

* Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
† 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 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 optimal 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 4.0.
CTCAE=Common Terminology Criteria for Adverse Events.

Permanently discontinue IBRANCE in patients with severe interstitial lung disease (ILD)/pneumonitis.

Refer to the Full Prescribing Information for coadministered endocrine therapy and/or inavolisib 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 to 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)].*

Dose Modifications for Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive

days followed by 7 days off treatment to comprise a complete cycle of 28 days *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

3 DOSAGE FORMS AND STRENGTHS

125 mg tablets: Oval, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 125" on the other side.

100 mg tablets: Oval, green, film-coated tablets debossed with "Pfizer" on one side and "PBC 100" on the other side.

75 mg tablets: Round, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 75" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 with an incidence of 80% and PALOMA-3 with an incidence of 83%. A Grade ≥3 decrease in neutrophil counts was reported in 66% of patients receiving IBRANCE plus letrozole in PALOMA-2 and 66% of patients receiving IBRANCE plus fulvestrant in PALOMA-3. In PALOMA-2 and PALOMA-3, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥3 neutropenia was 7 days *[see Adverse Reactions (6.1)]*.

Monitor complete blood counts prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 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)]*.

Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Physicians should inform patients to promptly report any episodes of fever *[see Patient Counseling Information (17)]*.

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including IBRANCE when taken in combination with endocrine therapy.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4 and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported *[see Adverse Reactions (6.2)]*.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia,

cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis *[see Dosage and Administration (2.2)]*.

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose *[see Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neutropenia *[see Warnings and Precautions (5.1)]*
- ILD/Pneumonitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Studies Experience

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

PALOMA-2: IBRANCE plus Letrozole

Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in PALOMA-2. The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in PALOMA-2. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 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 PALOMA-2.

Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (10%) patients receiving IBRANCE plus letrozole and in 13 of 222 (6%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving IBRANCE plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections,

leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse reactions (≥10%) reported in patients who received IBRANCE plus letrozole or placebo plus letrozole in PALOMA-2 are listed in Table 4.

Table 4. Adverse Reactions (≥10%) in PALOMA-2

	IBRANCE plus Letrozole (N=444)			**Placebo plus Letrozole (N=222)**		
Adverse Reaction	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and infestations						
Infections*	60†	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis‡	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33§	N/A	N/A	16¶	N/A	N/A
Rash#	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable;

* Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
† Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza,

pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.

‡ Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

§ Grade 1 events – 30%; Grade 2 events – 3%.

¶ Grade 1 events – 15%; Grade 2 events – 1%.

Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Clinically relevant adverse reactions in <10% of patients who received IBRANCE plus letrozole in PALOMA-2 included epistaxis (9%), lacrimation increased (6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

Table 5. Laboratory Abnormalities in PALOMA-2

	IBRANCE plus Letrozole (N=444)			**Placebo plus Letrozole (N=222)**		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
WBC decreased	97	35	1	25	1	0
Blood creatinine increased	96	2	<1	91	0	0
Neutrophils decreased	95	56	12	20	1	1
Hemoglobin decreased	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0
Alanine aminotransferase increased	43	2	<1	30	0	0

N=number of patients; WBC=white blood cells.

PALOMA-3: IBRANCE plus Fulvestrant

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in PALOMA-3. The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in PALOMA-3. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months.

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 discontinuation for those patients receiving IBRANCE plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

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

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus fulvestrant in descending frequency were neutropenia and leukopenia.

Adverse reactions (≥10%) reported in patients who received IBRANCE plus fulvestrant or placebo plus fulvestrant in PALOMA-3 are listed in Table 6.

Table 6. Adverse Reactions (≥10%) 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*	47†	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis‡	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18§	N/A	N/A	6¶	N/A	N/A
Rash#	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.
* Infections includes all reported preferred terms (PTs) that are part of the System Organ Class

Infections and infestations.
† Most common infections (≥1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, bronchitis, rhinitis, influenza, conjunctivitis, sinusitis, pneumonia, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, and paronychia.
‡ Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
§ Grade 1 events – 17%; Grade 2 events – 1%.
¶ Grade 1 events – 6%.
# Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Clinically relevant adverse reactions in <10% of patients who received IBRANCE plus fulvestrant in PALOMA-3 included asthenia (8%), dysgeusia (7%), epistaxis (7%), lacrimation increased (6%), dry skin (6%), vision blurred (6%), dry eye (3.8%), and febrile neutropenia (0.9%).

Table 7. Laboratory Abnormalities in PALOMA-3

Laboratory Abnormality	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Blood creatinine increased	95	1	0	82	0	0
Hemoglobin decreased	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

N=number of patients; WBC=white blood cells.

INAVO120: IBRANCE plus Inavolisib and Fulvestrant

Adults with PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease

The safety of the combination of IBRANCE plus inavolisib and fulvestrant was evaluated in a randomized, double-blind, placebo-controlled study (INAVO120) in 324 patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast

cancer *[see Clinical Studies (14)]*.

Patients received either IBRANCE 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days plus fulvestrant in combination with inavolisib (n=162) or placebo (n=162). The median duration of treatment for IBRANCE plus inavolisib and fulvestrant was 9 months (range: 0 to 39 months).

Serious adverse reactions occurred in 24% of patients who received IBRANCE plus inavolisib and fulvestrant. Serious adverse reactions occurring in ≥1% of patients receiving IBRANCE plus inavolisib and fulvestrant included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%).

Fatal adverse reactions occurred in 3.7% of patients who received IBRANCE plus inavolisib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage.

Permanent discontinuation of IBRANCE associated with an adverse reaction occurred in 8 of 162 (4.9%) patients receiving IBRANCE plus inavolisib and fulvestrant and in 0 of 162 patients receiving IBRANCE plus placebo and fulvestrant. Adverse reactions leading to discontinuation of IBRANCE in patients receiving IBRANCE plus inavolisib and fulvestrant were neutropenia, infections, alanine aminotransferase increased, gastric ulcer, intestinal perforation, hyperglycemia, type 2 diabetes mellitus, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury (0.6% each).

Dose reduction of IBRANCE due to an adverse reaction occurred in 38% of patients receiving IBRANCE plus inavolisib and fulvestrant and in 30% of patients receiving IBRANCE plus placebo and fulvestrant. Adverse reactions leading to dose reductions of IBRANCE in ≥2% patients receiving IBRANCE plus inavolisib and fulvestrant were neutropenia (30%), leukopenia (6%), and thrombocytopenia (3.7%).

Dose interruption of IBRANCE due to an adverse reaction occurred in 71% of patients receiving IBRANCE plus inavolisib and fulvestrant and in 61% of patients receiving IBRANCE plus placebo and fulvestrant. Adverse reactions leading to dose interruption of IBRANCE in ≥2% patients receiving IBRANCE plus inavolisib and fulvestrant were neutropenia (56%), infections (29%), leukopenia (12%), stomatitis (4.9%), anemia (6%), thrombocytopenia (4.3%), diarrhea (3.7%), pyrexia (3.1%), alanine aminotransferase increased (2.5%), hyperglycemia (2.5%), and nausea (2.5%).

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased alanine aminotransferase (ALT), nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

Adverse reactions and laboratory abnormalities in INAVO120 are summarized in Table 8 and Table 9, respectively.

Table 8. Adverse Reactions (≥10% with ≥5% [All Grades] or ≥2% [Grade 3-4] Higher Incidence in the IBRANCE plus inavolisib and fulvestrant Arm) in INAVO120

Adverse Reaction	IBRANCE plus Inavolisib and Fulvestrant (N=162)		IBRANCE plus Placebo and Fulvestrant (N=162)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Stomatitis*	51	6†	27	0
Diarrhea	48	3.7†	16	0
Nausea	28	0.6†	17	0
Vomiting	15	0.6†	4.9	1.2†
General Disorders and Administration Site Conditions				
Fatigue	38	1.9†	25	1.2†
Skin and Subcutaneous Tissue Disorders				
Rash‡	26	0	19	0
Alopecia	19	0	6	0
Dry skin§	13	0	4.3	0
Metabolism and Nutrition Disorders				
Decreased appetite	24	0	9	0
Infections and Infestations				
COVID-19 infection	23	1.9	10	0.6
Urinary tract infection‡	15	1.2†	9	0
Nervous System Disorders				
Headache‡	22	0	14	0
Investigations				
Decreased weight	17	3.7†	0.6	0

* Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.
† No Grade 4 adverse reactions were observed.
‡ Includes other related terms.
§ Includes dry skin, skin fissures, xerosis, and xeroderma.

Clinically relevant adverse reactions occurring in <10% of patients who received the triplet combination of IBRANCE plus inavolisib and fulvestrant included abdominal pain, dry eye, dysgeusia, and dyspepsia.

Table 9. Select Laboratory Abnormalities (≥10% with a ≥2% [All Grades or Grade 3-4] Higher Incidence in the IBRANCE plus Inavolisib and Fulvestrant Arm) in INAVO120

Laboratory Abnormality	IBRANCE plus Inavolisib and Fulvestrant*		IBRANCE plus Placebo and Fulvestrant†	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Neutrophils (total, absolute) decreased	95	82	97	79
Hemoglobin decreased	88	8‡	85	2.5‡
Platelets decreased	8	16	71	3.7

Lymphocytes (absolute) decreased	72	9	68	14
Chemistry				
Glucose (fasting) increased[§]	85	12	43	0
Calcium decreased	42	3.1	32	3.7
Potassium decreased	38	6	21	0.6[‡]
Creatinine increased	38	1.9[‡]	30	1.2[‡]
ALT increased	34	3.1[‡]	29	1.2[‡]
Sodium decreased	28	2.5[‡]	19	2.5
Magnesium decreased	27	0.6	21	0
Lipase (fasting) increased	16	1.4[‡]	7	0

ALT=alanine aminotransferase.

* The denominator used to calculate the rate varied from 122 to 160 based on the number of patients with a baseline value and at least one post-treatment value.
† The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value.
‡ No Grade 4 laboratory abnormalities were observed.
§ Grading according to CTCAE version 4.03.

Other Clinical Trials Experience

The following adverse reaction has been reported following administration of IBRANCE: venous thromboembolism.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IBRANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory Disorders: Interstitial lung disease (ILD)/non-infectious pneumonitis

Skin and Subcutaneous Tissue Disorders: Palmar-plantar erythrodysesthesia syndrome (PPES)

Male Patients with HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer

Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.

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, 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, enzalutamide, and St John's Wort) *[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 to 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 its exposure *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on AUC *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

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 of palbociclib up to 300 mg/kg/day and 20 mg/kg/day, 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, respectively.

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 is no information regarding the presence of palbociclib in human milk, its effects on milk production, or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from IBRANCE, advise a lactating woman not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, IBRANCE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].* Females of reproductive potential should have a pregnancy test prior to starting treatment with IBRANCE.

Contraception

Females

IBRANCE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on animal studies, IBRANCE may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of IBRANCE in pediatric patients have not been established.

The safety and effectiveness of IBRANCE were assessed but not established in three trials: one open-label trial [A5481092, (NCT03709680)] that included 98 pediatric patients 2 to <17 years of age who received IBRANCE in combination with chemotherapy for recurrent or refractory solid tumors and two open-label trials that included 42 pediatric patients 4 to <17 years of age who received IBRANCE as a single agent for recurrent or refractory solid tumors [APEC1621I, (NCT03526250)] or primary central nervous system (CNS) tumors [PBTC-042, (NCT02255461)].

No new safety signals were observed in these trials. Palbociclib exposures in pediatric patients who received IBRANCE as a single agent or in combination were within range of those observed in adults given a similar dose based on body surface area.

Juvenile Animal Toxicity Data

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

Toxicities in teeth independent of altered glucose metabolism were observed in rats. Administration of 100 mg/kg palbociclib for 27 weeks (approximately 15 times the adult human exposure [AUC] at the recommended dose) resulted in abnormalities in growing incisor teeth (discolored, ameloblast degeneration/necrosis, mononuclear cell infiltrate). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 Geriatric Use

Of 444 patients who received IBRANCE in PALOMA-2, 181 patients (41%) were ≥65 years of age and 48 patients (11%) were ≥75 years of age. Of 347 patients who received IBRANCE in PALOMA-3, 86 patients (25%) were ≥65 years of age and 27 patients (8%) were ≥75 years of age. No overall differences in safety or effectiveness of IBRANCE were observed between these patients and younger patients.

8.6 Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days *[see Dosage and Administration (2.2)]*. Based on a pharmacokinetic trial in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUC_{INF}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*.

Review the Full Prescribing Information for the aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

8.7 Renal Impairment

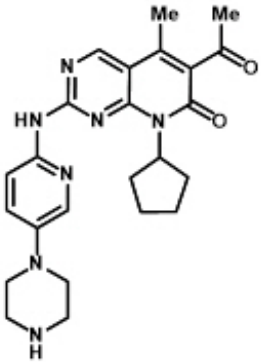
No dose adjustment is required in patients with mild, moderate, or severe renal impairment (CrCl >15 mL/min).

Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUC_{INF}) increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl <90 mL/min), moderate (30 mL/min ≤ CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function.

The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

IBRANCE tablets 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. 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, colloidal silicon dioxide, crospovidone, magnesium stearate, succinic acid, HPMC 2910/hypromellose, titanium dioxide, triacetin, and FD&C Blue #2/Indigo Carmine Aluminum Lake. In addition, the 75 mg and 125 mg tablets contain red iron oxide and the 100 mg tablets contain yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palbociclib is an inhibitor of cyclin-dependent kinases (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 (Rb) protein 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 led to increased cell senescence compared to each drug alone, which was sustained for up to 6 days following palbociclib removal and was greater if antiestrogen treatment was continued. 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.

Human bone marrow mononuclear cells treated with palbociclib in the presence or absence of an anti-estrogen in vitro did not become senescent and resumed proliferation following palbociclib withdrawal.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib had no large effect on QTc (i.e., >20 ms) at 125 mg once daily for 21 consecutive days

followed by 7 days off treatment to comprise a complete cycle of 28 days.

12.3 Pharmacokinetics

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

Absorption

The maximum observed concentration (C_{max}) of palbociclib is generally observed between 4 to 12 hours (time to reach maximum concentration, T_{max}) following oral administration of IBRANCE tablets. 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 to 4.2).

Food Effect: The area under the concentration-time curve from zero to infinity (AUC_{INF}) and C_{max} of palbociclib increased by 22% and 26%, respectively, when IBRANCE tablets were given with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), and by 9% and 10%, respectively, when IBRANCE tablets were given with a moderate-fat, standard-calorie meal (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively), compared to IBRANCE tablets given under overnight fasted conditions.

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 mean fraction unbound (f_u) of palbociclib in human plasma in vivo increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib f_u in human plasma in vivo with worsening renal function. The geometric mean apparent volume of distribution (V_Z/F) was 2583 L with a coefficient of variation (CV) of 26%.

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.

Specific Populations

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.

Hepatic Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic impairment indicate that palbociclib unbound AUC_{INF} decreased 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Palbociclib unbound C_{max} increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (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, further supporting the findings from the dedicated hepatic impairment study.

Renal Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that palbociclib AUC_{INF} increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl <90 mL/min), moderate (30 mL/min ≤ CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. In addition, 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 requiring hemodialysis.

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 *[see Drug Interactions (7.1)]*.

CYP3A Inducers: Data from a drug interaction trial in healthy subjects (N=15) indicate that coadministration of multiple 600 mg daily 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. Data from a drug interaction trial in healthy subjects (N=14) indicate 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 *[see Drug Interactions (7.2)]*.

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 to administration of midazolam alone *[see Drug Interactions (7.3)]*.

Gastric pH Elevating Medications: In a drug interaction trial in healthy subjects, coadministration of a single 125 mg IBRANCE tablet with multiple doses of the proton pump inhibitor (PPI) rabeprazole under overnight fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg IBRANCE tablet administered alone. Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, an effect of these classes of acid reducing agents on palbociclib exposure is not expected.

Effect of Palbociclib on Transporters: In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations. In vitro, palbociclib has the potential to inhibit OCT1 at clinically relevant concentrations, as well as the potential to inhibit P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) in the gastrointestinal tract at the proposed dose.

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

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Oral administration of palbociclib for 2 years resulted in an increased incidence of microglial cell tumors in the central nervous system of male rats at a dose of 30 mg/kg/day (approximately 8 times the human clinical exposure based on AUC). There were no neoplastic findings in female rats at doses up to 200 mg/kg/day (approximately 5 times the human clinical exposure based on AUC). Oral administration of palbociclib to male and female rasH2 transgenic mice for 6 months did not result in increased incidence of neoplasms at doses up to 60 mg/kg/day.

Palbociclib was aneugenic in Chinese Hamster Ovary cells in vitro and in the bone marrow of male rats at doses ≥100 mg/kg/day for 3 weeks. Palbociclib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic 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).

The adverse effects of palbociclib on male reproductive function and fertility were observed in the repeat-dose toxicology studies in rats and dogs and a male fertility study in rats. In repeat-dose toxicology studies, palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle at ≥30 mg/kg/day in rats and ≥0.2 mg/kg/day in dogs included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, and decreased secretion. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. These doses in rats and dogs resulted in approximately ≥10 and 0.1 times, respectively, the exposure [AUC] in humans at the recommended dose. In the fertility and early embryonic development study in male rats, palbociclib caused no effects on mating but resulted in a slight decrease in fertility in association with lower sperm motility and density at 100 mg/kg/day with projected exposure levels [AUC] of 20 times the exposure in humans at the recommended dose.

14 CLINICAL STUDIES

PALOMA-2: IBRANCE plus Letrozole

Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy

PALOMA-2 was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus letrozole versus placebo plus letrozole 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 666 patients were randomized 2:1 to IBRANCE plus letrozole or placebo plus letrozole. Randomization was stratified by disease site (visceral versus non-visceral), disease-free interval (de novo metastatic versus ≤12 months from the end of adjuvant treatment to disease recurrence versus >12 months from the end of adjuvant treatment to disease recurrence), and nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapies versus no prior hormonal therapy). 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 objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by the investigator according to RECIST Version 1.1 and overall survival (OS).

Patients enrolled in this study had a median age of 62 years (range 28 to 89). The majority of patients were White (78%), and most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (98%). Forty-eight percent of patients had received chemotherapy and 56% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Thirty-seven percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (97%) had metastatic disease. Twenty-three percent of patients had bone only disease, and 49% of patients had visceral disease.

Major efficacy results from PALOMA-2 are summarized in Table 10 and Figure 1. Consistent results were observed across patient subgroups of disease-free interval (DFI), disease site, and prior therapy. The treatment effect of the combination on PFS was also supported by an independent review of radiographs. Based on the prespecified final OS analysis conducted after 435 events, OS was not statistically significant.

Table 10. Efficacy Results – PALOMA-2

	IBRANCE plus Letrozole	**Placebo plus Letrozole**
Progression-free survival for ITT (investigator assessment)	**N=444**	**N=222**
Number of PFS events (%)	194 (43.7)	137 (61.7)
Median progression-free survival (months, 95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio (95% CI) and p-value	0.576 (0.463, 0.718)*, p<0.0001†	
Objective Response for patients with measurable disease (investigator assessment)	**N=338**	**N=171**
Objective response rate‡ (%, 95% CI)	55.3 (49.9, 60.7)	44.4 (36.9, 52.2)
Overall survival for ITT	**N=444**	**N=222**
Number of OS events (%)	287 (64.6)	148 (66.7)
Median OS (months, 95% CI)	53.8 (49.8, 59.2)	49.8 (42.3, 56.4)
Hazard ratio (95% CI) and p-value	0.921 (0.755, 1.124)*, p=0.2087†	

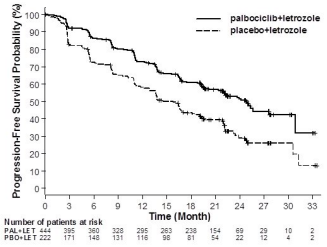
CI=confidence interval; ITT=Intent-to-Treat; N=number of patients; NE=not estimable; OS=Overall survival; PFS=Progression-free survival.

* Cox proportional hazards model stratified by disease site (visceral vs. non-visceral) per randomization.

† Stratified log-rank test one-sided p-value.

‡ Response is based on confirmed responses.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival – PALOMA-2 (Investigator Assessment, Intent-to-Treat Population)



LET=letrozole;
PAL=palbociclib;
PBO=placebo.

PALOMA-3: IBRANCE plus Fulvestrant

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

PALOMA-3 was an international, randomized, double-blind, parallel-group, multicenter study of IBRANCE plus fulvestrant versus placebo plus fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. A total of 521 pre/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. 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. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients on study were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy, and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS and final OS from PALOMA-3 are summarized in Table 11. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively. Consistent PFS results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. After a median follow-up time of 45 months, the final OS results were not statistically significant.

Table 11. Efficacy Results – PALOMA-3

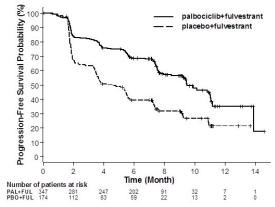
	IBRANCE plus Fulvestrant	**Placebo plus Fulvestrant**
Progression-free survival for	**N=347**	**N=174**

ITT (investigator assessment)		
Number of PFS events (%)	145 (41.8)	114 (65.5)
Median PFS (months, 95% CI)	9.5 (9.2, 11.0)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.461 (0.360, 0.591), p<0.0001	
Objective Response for patients with measurable disease (investigator assessment)	**N=267**	**N=138**
Objective response rate* (%, 95% CI)	24.6 (19.6, 30.2)	10.9 (6.2, 17.3)
Overall survival for ITT	**N=347**	**N=174**
Number of OS events (%)	201 (57.9)	109 (62.6)
Median OS (months, 95% CI)	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value	0.814 (0.644, 1.029), p=0.0857†‡	

CI=confidence interval; ITT=Intent-to-Treat; N=number of patients; OS=overall survival; PFS=progression-free survival.

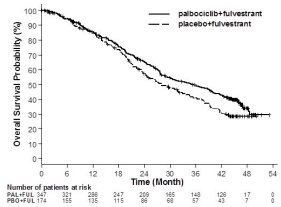
* Responses are based on confirmed responses.
† Not statistically significant at the pre-specified 2-sided alpha level of 0.047.
‡ 2-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomization.

Figure 2. Kaplan-Meier Plot of Progression-Free Survival – PALOMA-3 (Investigator Assessment, Intent-to-Treat Population)



FUL=fulvestrant;
PAL=palbociclib;
PBO=placebo.

Figure 3. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-3



FUL=fulvestrant;
PAL=palbociclib;
PBO=placebo.

INAVO120: IBRANCE plus Inavolisib and Fulvestrant

Adults with PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease

INAVO120 (NCT04191499) was a randomized (1:1), double-blind, placebo-controlled trial evaluating the efficacy of inavolisib in combination with IBRANCE and fulvestrant in adult patients with endocrine-resistant *PIK3CA*-mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

Patients were required to have a HbA_{1C} <6% and fasting blood glucose <126 mg/dL. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment at the start of study treatment.

PIK3CA mutation status was prospectively determined in a central laboratory using the FoundationOne® Liquid CDx assay on plasma-derived circulating tumor DNA (ctDNA) or in local laboratories using various validated polymerase chain reaction (PCR) or next-generation sequencing (NGS) assays on tumor tissue or plasma. All patients were required to provide both a freshly collected pre-treatment blood sample and a tumor tissue sample for central evaluation and determination of *PIK3CA* mutation(s) status.

Patients received either inavolisib 9 mg (n=161) or placebo (n=164) orally once daily, in combination with IBRANCE 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days, and fulvestrant 500 mg administered intramuscularly on Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle. Patients received treatment until disease progression or unacceptable toxicity. In addition, all pre/perimenopausal women and men received an LHRH agonist throughout therapy.

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98% female, of which 39% were pre/perimenopausal; 59% White, 38% Asian, 2.5% Unknown, 0.6% Black or African American; 6% Hispanic or Latino; and ECOG PS of 0 (63%) or 1 (36%). Tamoxifen (57%) and aromatase inhibitors (50%) were the most commonly used adjuvant endocrine therapies. Sixty-four percent of patients were considered to have secondary endocrine resistance. Eighty-three percent of patients had received prior chemotherapy (in the neo/adjuvant setting) and 1.2% of patients had been treated with a CDK4/6 inhibitor.

The major efficacy outcome measure was investigator (INV)-assessed PFS per RECIST version 1.1. Additional efficacy outcome measures included OS, INV-assessed ORR, and INV-assessed duration of response (DOR).

Efficacy results are summarized in Table 12 and Figure 4. INV-assessed PFS results

were supported by consistent results from a blinded independent central review (BICR) assessment. At the time of the PFS analysis, OS data were not mature with 30% deaths in the overall population.

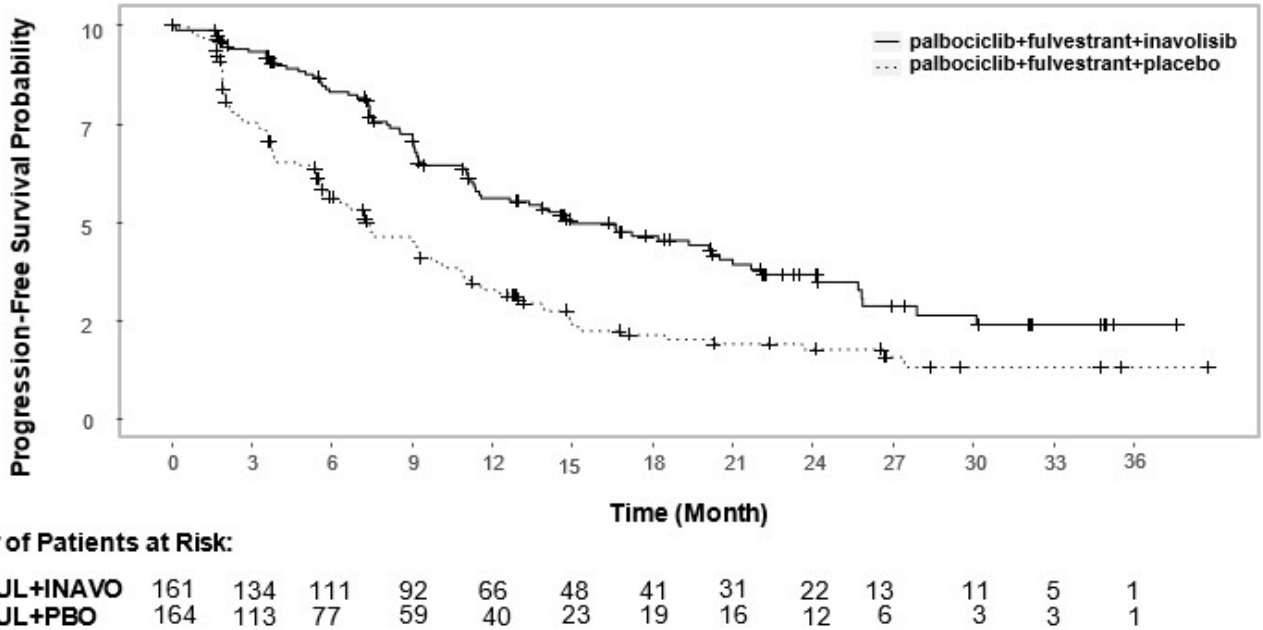
Table 12. Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120

Efficacy Endpoint	IBRANCE plus Inavolisib and Fulvestrant N=161	IBRANCE plus Placebo and Fulvestrant N=164
Progression-Free Survival[*†]		
Patients with event (%)	82 (51)	113 (69)
Median, months (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	<0.0001	
Objective Response Rate[*†‡]		
Patients with CR or PR (%)	94 (58)	41 (25)
95% CI	(50, 66)	(19, 32)
Duration of Response[†]		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)

CI=confidence interval; CR=complete response; DOR=duration of response; N=number of patients; PR=partial response.

* Per RECIST version 1.1.
† Based on investigator assessment.
‡ Based on confirmed ORR.

Figure 4. Kaplan-Meier Curve for Investigator-Assessed Progression-Free Survival in INAVO120



16 HOW SUPPLIED/STORAGE AND HANDLING

IBRANCE is supplied in the following strengths and package configurations:

IBRANCE Tablets

Package Configuration	Tablet Strength (mg)	NDC	Tablet Description
Monthly box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	125	NDC 0069-0688-03	Oval, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 125" on the other side.
Monthly box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	100	NDC 0069-0486-03	Oval, green, film-coated tablets debossed with "Pfizer" on one side and "PBC 100" on the other side.
Monthly box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	75	NDC 0069-0284-03	Round, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 75" on the other side.

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) *[see USP Controlled Room Temperature]*. Store in the original blister pack.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression/Infection

- 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 (5.1)]*.

Interstitial Lung Disease/Pneumonitis

- Advise patients to immediately report new or worsening respiratory symptoms *[see Warnings and Precautions (5.2)]*.

Drug Interactions

- Grapefruit may interact with IBRANCE. 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 healthcare providers of all concomitant medications,

including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.

Dosing and Administration

- Inform patients that IBRANCE tablets may be taken with or without food.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE tablets should be swallowed whole (do not chew, crush, or split them prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.
- Pre/perimenopausal women treated with IBRANCE should also be treated with LHRH agonists *[see Dosage and Administration (2.1)]*.
- When IBRANCE is used in combination, refer to the other products' Full Prescribing Information for dosing and administration information *[see Dosage and Administration (2.1, 2.2)]*.

Pregnancy, Lactation, and Infertility

- Embryo-Fetal Toxicity
    - Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with IBRANCE therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1 and 8.3)]*.
    - Advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 months after the last dose *[see Use in Specific Populations (8.3)].*
- Lactation: Advise women not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose *[see Use in Specific Populations (8.2)].*
- Infertility: Inform males of reproductive potential that IBRANCE may cause infertility and to consider sperm preservation before taking IBRANCE *[see Use in Specific Populations (8.3)]*.

This product's labeling may have been updated. For full prescribing information, please visit www.pfizer.com. For medical information about IBRANCE, please visit www.pfizermedinfo.com or call 1-800-438-1985.

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

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

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 very common when taking IBRANCE and may cause serious infections that can lead to death. 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 cycle. Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections such as fever and chills.
Lung problems (pneumonitis). IBRANCE may cause severe or life-threatening inflammation of the lungs during treatment that can lead to death. Tell your healthcare provider right away if you have any new or worsening symptoms, including:

- chest pain
- cough with or without mucus
- trouble breathing or shortness of breath

Your healthcare provider may interrupt or stop treatment with IBRANCE completely if your symptoms are severe.
See "What are the possible side effects of IBRANCE?" for more information about side effects.

What is IBRANCE?
IBRANCE is a prescription medicine used:
In adults to treat hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has spread to other parts of the body (metastatic) in combination with:

- an aromatase inhibitor as the first hormonal based therapy, or
- fulvestrant in people with disease progression following hormonal therapy.

In adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative and with an abnormal phosphatidylinositol-3-kinase catalytic subunit alpha *(PIK3CA)* gene breast cancer that has spread to nearby tissue or lymph nodes (locally advanced), or to other parts of the body (metastatic) in combination with:

- inavolisib and fulvestrant in people with disease progression during or after adjuvant hormonal therapy.

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

What should I tell my healthcare provider before taking IBRANCE?
Before taking IBRANCE, tell your healthcare provider about all of your medical conditions, including 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 should use effective birth control during treatment and for at least 3 weeks after the last dose of IBRANCE. Your healthcare provider may ask you to take a pregnancy test before you start treatment with IBRANCE.
    - **Males** with female partners who can become pregnant should use effective birth control during treatment with IBRANCE for at least 3 months after the last dose of 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. Do not breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

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.
- IBRANCE tablets may be taken with or without food.
- IBRANCE should be taken at about the same time each day.
- Swallow IBRANCE tablets whole. Do not chew, crush or split IBRANCE tablets before swallowing them.
- Do not take any IBRANCE tablets 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.
- When IBRANCE is used in combination with inavolisib and fulvestrant, or an aromatase inhibitor, also read the Patient Information for the prescribed products.

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?"
The most common side effects of IBRANCE when used with either letrozole or fulvestrant include:

- 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

- infections (see "What is the most important information I should know about IBRANCE?")
- tiredness
- nausea
- sore mouth
- abnormalities in liver blood tests
- diarrhea
- hair thinning or hair loss
- increased blood creatinine

The most common side effects when inavolisib is added to IBRANCE plus fulvestrant include:

- high blood sugar levels leading to excessive thirst and urination
- sore mouth
- diarrhea
- decreased white blood cell counts, red blood cell counts, and platelet counts
- decreased blood levels of calcium, potassium, sodium, and magnesium
- increased creatine blood levels
- tiredness
- abnormalities in liver blood tests
- nausea
- rash
- loss of appetite
- COVID-19 infection
- headache

IBRANCE may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider about family planning options before starting IBRANCE if this is a concern for you.
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.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store IBRANCE?

- Store IBRANCE at 68 °F to 77 °F (20 °C to 25 °C) in the original blister pack.

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. You can ask your pharmacist or healthcare provider for more information about IBRANCE that is written for health professionals.

What are the ingredients in IBRANCE?

Active ingredient: palbociclib

Inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, succinic acid, HPMC 2910/hypromellose, titanium dioxide, triacetin, and FD&C Blue #2/Indigo Carmine Aluminum Lake. In addition, the 75 mg and 125 mg tablets contain red iron oxide and the 100 mg tablets contain yellow iron oxide.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Distributed by
Pfizer Labs
Division of Pfizer Inc.
New York, NY 10001

LAB-1372-7.0

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: September 2025

PRINCIPAL DISPLAY PANEL - 75 mg Tablet Dose Pack

PROFESSIONAL SAMPLE - NOT FOR SALE

Pfizer

NDC 63539-284-07

IBRANCE®
(palbociclib)

tablets

75 mg per tablet

This weekly pack contains:
7 tablets

Rx only

PRINCIPAL DISPLAY PANEL - 75 mg Tablet Dose Pack Box

PROFESSIONAL SAMPLE - NOT FOR SALE

Pfizer

NDC 63539-284-03

IBRANCE®
(palbociclib)

tablets

75 mg

21 tablets

Monthly Box Contains: 3 individual weekly packs. Each pack contains 7 IBRANCE tablets (75 mg per tablet).

Rx only

Safety
Label

PROFESSIONAL SAMPLE - NOT FOR SALE

NDC 63539-284-03

IBRANCE®
(palbociclib)
tablets

75 mg

21 tablets

Monthly Box Contains: 3 individual weekly packs. Each pack contains 7 IBRANCE tablets (75 mg per tablet).

Rx only

Safety Label

DOSAGE AND USE
Please see accompanying Prescribing Information and Patient Information.

Each tablet contains 75 mg of palbociclib.

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

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017
MADE IN IRELAND

PAA135220

IBRANCE®
(palbociclib)
tablets
75 mg

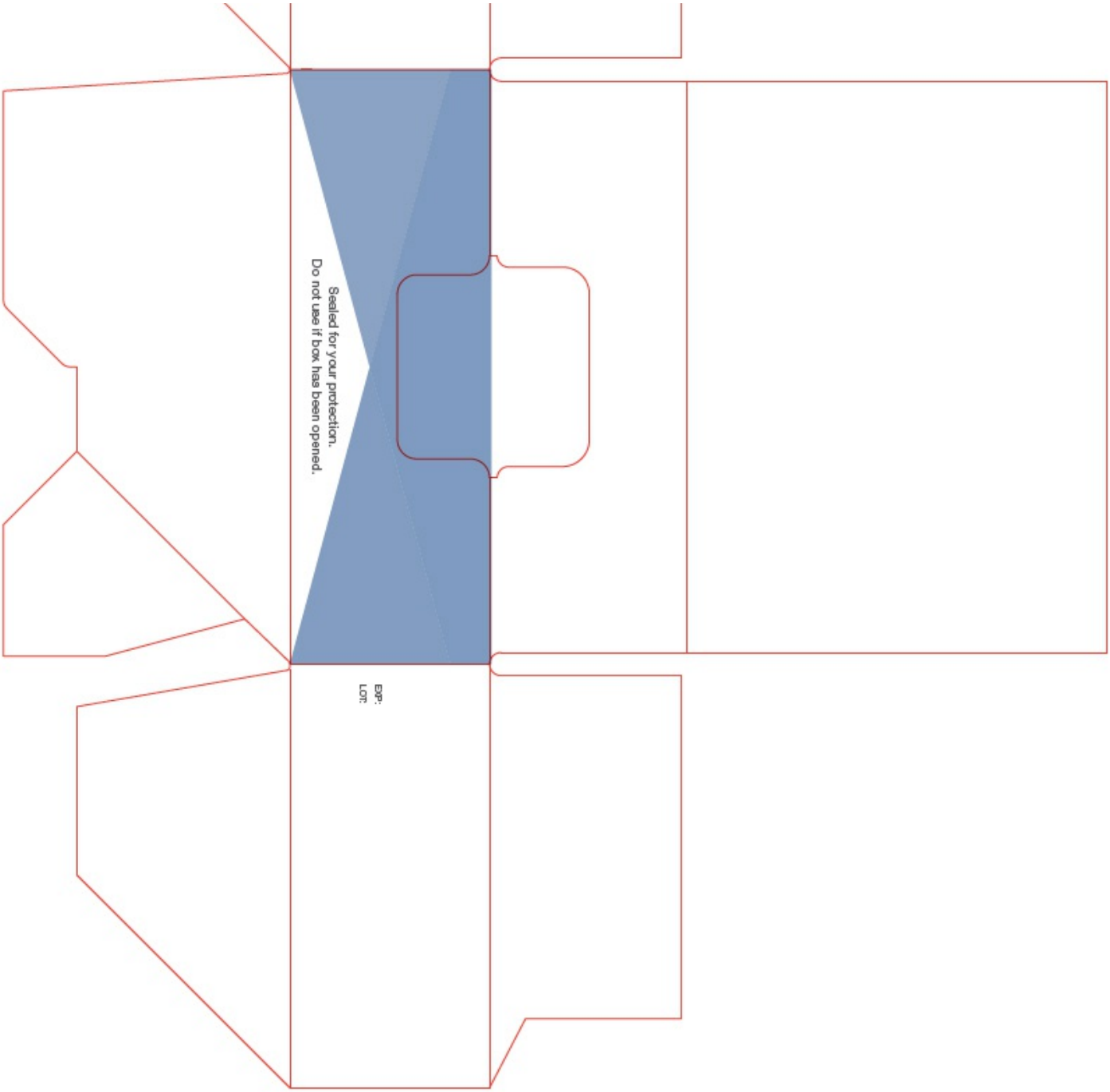
For more information,
go to www.IBRANCE.com or call 1-800-438-1985.

Take IBRANCE exactly as your healthcare provider tells you.

Take 1 IBRANCE tablet, once daily, for 21 consecutive days followed by 7 days off treatment.

IBRANCE®
(palbociclib)
tablets

75 mg



PRINCIPAL DISPLAY PANEL - 100 mg Tablet Dose Pack

PROFESSIONAL SAMPLE - NOT FOR SALE

Pfizer

NDC 63539-486-07

IBRANCE®
(palbociclib)

tablets

100 mg per tablet

This weekly pack contains:

7 tablets

Rx only

PRINCIPAL DISPLAY PANEL - 100 mg Tablet Dose Pack Box

PROFESSIONAL SAMPLE - NOT FOR SALE

Pfizer

NDC 63539-486-03

IBRANCE®
(palbociclib)

tablets

100 mg

21 tablets

Monthly Box Contains: 3 individual weekly packs. Each pack contains 7 IBRANCE tablets (100 mg per tablet).

Rx only

Safety
Label

PROFESSIONAL SAMPLE - NOT FOR SALE

NDC 63539-486-03

IBRANCE®
(palbociclib)
tablets

100 mg

21 tablets

Monthly Box Contains: 3 individual weekly packs. Each pack contains 7 IBRANCE tablets (100 mg per tablet).

Rx only

Safety Label

DOSAGE AND USE
Please see accompanying Prescribing Information and Patient Information.
Each tablet contains 100 mg of palbociclib.

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

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017
MADE IN IRELAND

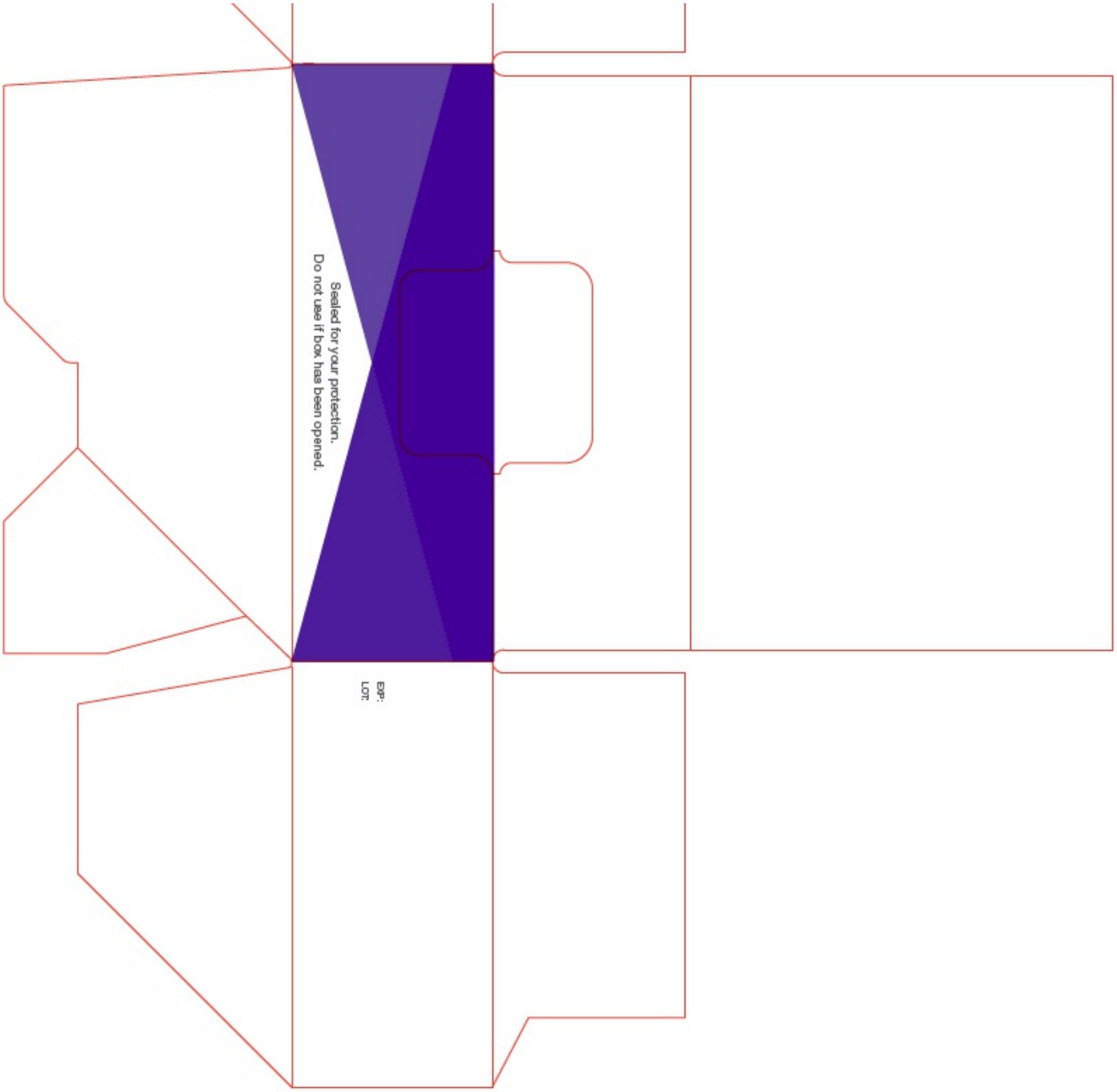
PAA135928

IBRANCE®
(palbociclib)
tablets
100 mg

Take 1 IBRANCE tablet, once daily, for 21 consecutive days followed by 7 days off treatment.

Take IBRANCE exactly as your healthcare provider tells you.

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



PRINCIPAL DISPLAY PANEL - 125 mg Tablet Dose Pack

PROFESSIONAL SAMPLE - NOT FOR SALE

Pfizer

NDC 63539-688-07

IBRANCE®
(palbociclib)

tablets

125 mg per tablet

This weekly pack contains:

7 tablets

Rx only

PRINCIPAL DISPLAY PANEL - 125 mg Tablet Dose Pack Box

PROFESSIONAL SAMPLE - NOT FOR SALE

Pfizer

NDC 63539-688-03

IBRANCE®
(palbociclib)

tablets

125 mg

21 tablets

Monthly Box Contains: 3 individual weekly packs. Each pack contains 7 IBRANCE tablets (125 mg per tablet).

Rx only

Safety
Label

PROFESSIONAL SAMPLE - NOT FOR SALE

NDC 63539-688-03

IBRANCE®
(palbociclib)
tablets

125 mg

21 tablets

Monthly Box Contains: 3 individual weekly packs. Each pack contains 7 IBRANCE tablets (125 mg per tablet).

Rx only

Safety Label

DOSAGE AND USE
Please see accompanying Prescribing Information and Patient Information.

Each tablet contains 125 mg of palbociclib.

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

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017
MADE IN IRELAND

PAA135927

IBRANCE®
(palbociclib)
tablets
125 mg

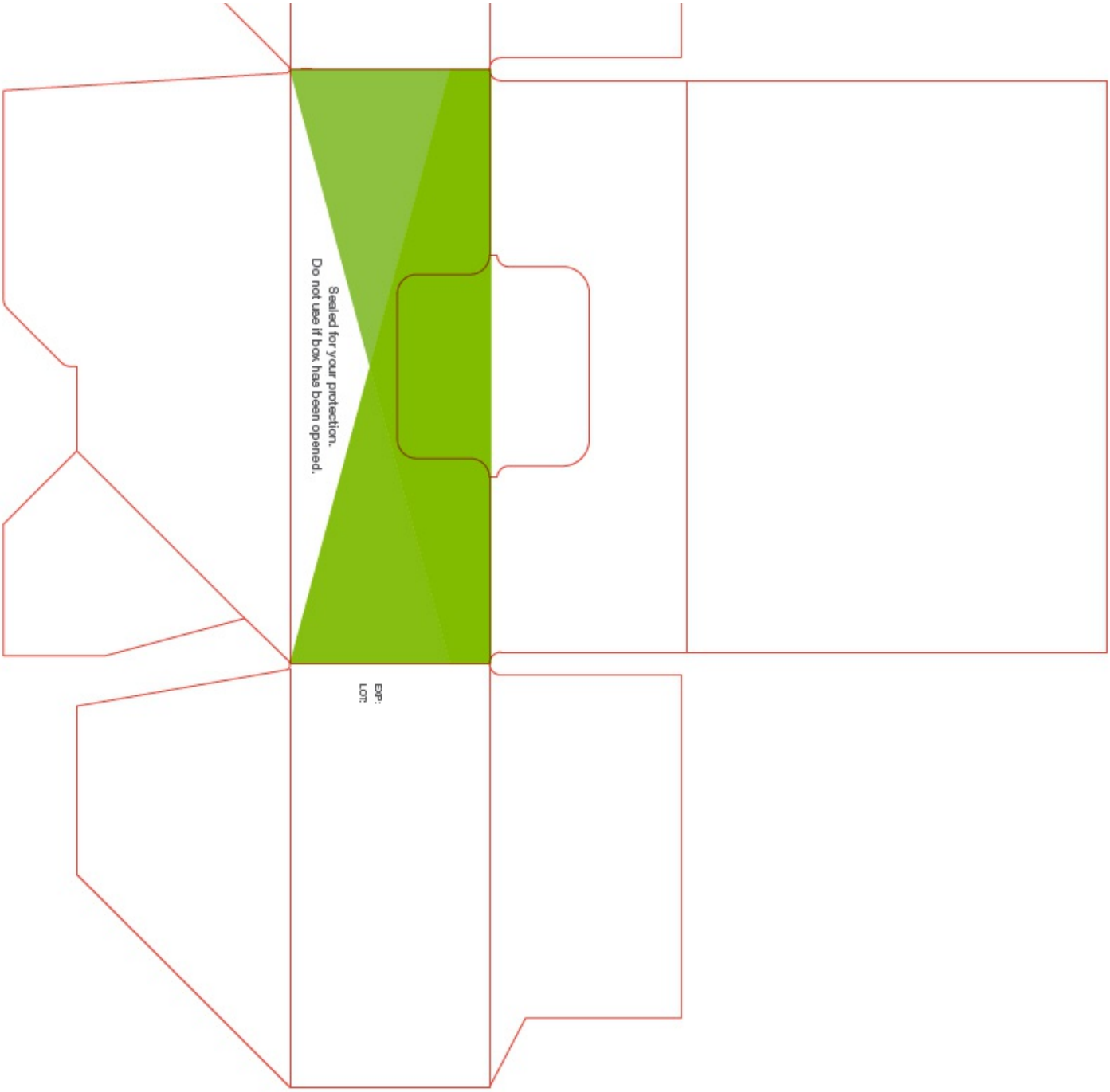
125 mg

IBRANCE®
(palbociclib)
tablets

Take 1 IBRANCE tablet, once daily, for 21 consecutive days followed by 7 days off treatment.

Take IBRANCE exactly as your healthcare provider tells you.

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



PRINCIPAL DISPLAY PANEL - Topper Card

Your Monthly Box

Includes 3 weekly packs of
IBRANCE® (palbociclib) medication.

Fill in the dates below to help track your treatment cycle.

Treatment Cycle

Week 1 Week 2 Week 3
IBRANCE

Week 4
No IBRANCE

My Treatment Cycle Tracker

I start my Week 1
treatment cycle on:
_____ / _____
MONTH DAY

After Week 4, I will start my
next treatment cycle on:
_____ / _____
MONTH DAY

PAA119239

Your Monthly Box

Includes **3 weekly packs** of
IBRANCE® (palbociclib) medication.
Fill in the dates below to **help track your treatment cycle.**

Treatment Cycle

My Treatment Cycle Tracker

I start my Week 1 **treatment cycle** on:

_____ / _____
MONTH DAY

After Week 4, I will start my **next treatment cycle** on:

_____ / _____
MONTH DAY

PAA119239

IBRANCE

palbociclib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63539-284
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PALBOCICLIB (UNII: G9ZF61LE7G) (PALBOCICLIB - UNII:G9ZF61LE7G)	PALBOCICLIB	75 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
CROSPOVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
SUCCINIC ACID (UNII: AB6MNQ6J6L)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
TRIACETIN (UNII: XHX3C3X673)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	PURPLE	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	Pfizer;PBC;75
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63539-284-03	3 in 1 CARTON	03/30/2020	
1	NDC:63539-284-07	7 in 1 DOSE PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

NDA	NDA212436	03/30/2020	

IBRANCE

palbociclib tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63539-486
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PALBOCICLIB (UNII: G9ZF61LE7G) (PALBOCICLIB - UNII:G9ZF61LE7G)	PALBOCICLIB	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
CROSPOVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
SUCCINIC ACID (UNII: AB6MNQ6J6L)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
TRIACETIN (UNII: XHX3C3X673)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics			
Color	GREEN	**Score**	no score
Shape	OVAL	**Size**	15mm
Flavor		**Imprint Code**	Pfizer;PBC;100
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63539-486-03	3 in 1 CARTON	03/30/2020	
1	NDC:63539-486-07	7 in 1 DOSE PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212436	03/30/2020	

IBRANCE

palbociclib tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63539-688
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PALBOCICLIB (UNII: G9ZF61LE7G) (PALBOCICLIB - UNII:G9ZF61LE7G)	PALBOCICLIB	125 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
CROSPOVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
SUCCINIC ACID (UNII: AB6MNQ6J6L)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
TRIACETIN (UNII: XHX3C3X673)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	PURPLE	**Score**	no score
Shape	OVAL	**Size**	16mm
Flavor		**Imprint Code**	Pfizer;PBC;125
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63539-688-03	3 in 1 CARTON	03/30/2020	
1	NDC:63539-688-07	7 in 1 DOSE PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212436	03/30/2020	

Labeler - U.S. Pharmaceuticals (829076905)

Establishment

Name	Address	ID/FEI	Business Operations
Viatris Pharmaceuticals LLC		829084552	ANALYSIS(63539-284, 63539-486, 63539-688) , LABEL(63539-284, 63539-486, 63539-688) , PACK(63539-284, 63539-486, 63539-688)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Ireland Pharmaceuticals Unlimited Company		985052076	ANALYSIS(63539-284, 63539-486, 63539-688) , API MANUFACTURE(63539-284, 63539-486, 63539-688)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Manufacturing Deutschland GmbH		341970073	ANALYSIS(63539-284, 63539-486, 63539-688) , MANUFACTURE(63539-284, 63539-486, 63539-688) , PACK(63539-284, 63539-486, 63539-688) , LABEL(63539-284, 63539-486, 63539-688)

Revised: 10/2025 U.S. Pharmaceuticals