PT. Pfizer Indonesia
Local Product Document

Generic Name: Palbociclib
Trade Name: Ibrance
CDS Effective Date: July 29, 2024
Supersedes: February 16, 2024

1. NAME OF THE MEDICINAL PRODUCT

1.1. Product name

IBRANCE®

1.2. Strength

75 mg, 100 mg, and 125 mg

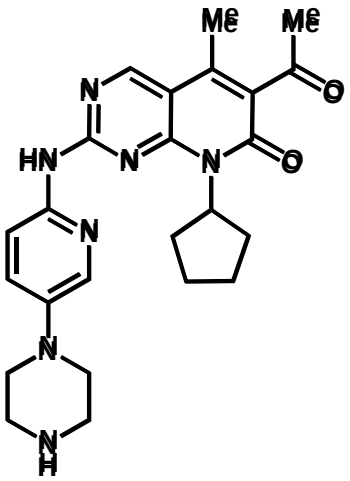
1.3. Pharmaceutical dosage form

Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration

Each film-coated tablet contains 75 mg or 100 mg or 125 mg of palbociclib freebase.



Palbociclib is a yellow to orange powder with a pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen).

2.2. Quantitative declaration

Excipients: see Section 6.1 List of excipients for the full list of excipients.

3. PHARMACEUTICAL FORM

Ibrance 75 mg: Round light purple film-coated tablet with “Pfizer” debossed on one tablet face and “PBC 75” debossed on the opposite tablet face.

Ibrance 100 mg: Oval green film-coated tablet with “Pfizer” debossed on one tablet face and “PBC 100” debossed on the opposite tablet face.

Ibrance 125 mg: Oval light purple film-coated tablet with “Pfizer” debossed on one tablet face and “PBC 125” debossed on the opposite tablet face.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

IBRANCE is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with letrozole with proven diagnosis of adenocarcinoma of the breast with evidence of loco regionally recurrent or metastatic disease not amenable to resection or radiation.
- in combination with fulvestrant in women who have received prior endocrine therapy (see Section 5.1 Pharmacodynamic properties).

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

4.2. Posology and method of administration

Treatment with IBRANCE should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

The recommended dose of IBRANCE is a 125 mg tablet taken orally once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days.

When co-administered with palbociclib, the recommended dose of letrozole is 2.5 mg taken orally once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of letrozole.

When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Treatment of pre or perimenopausal women with the combination of palbociclib plus an aromatase inhibitor/fulvestrant should always be combined with an LHRH agonist (see Section 4.4 Special warnings and precautions for use).

Patients should be encouraged to take their dose at approximately the same time each day. Continue the treatment as long as the patient is deriving clinical benefit from therapy.

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 the tablets prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Method of administration

IBRANCE is for oral use. IBRANCE tablets may be taken with or without food. Palbociclib should not be taken with grapefruit or grapefruit juice (see Section 4.5 Interaction with other medicinal products and other forms of interaction). IBRANCE tablets should be swallowed whole (should not be chewed, crushed, or split the tablets prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Dose modifications

Dose modification of IBRANCE is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dosing interruptions/cycle delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Table 1, Table 2, and Table 3 (see Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects).

Table 1. IBRANCE Recommended Dose Modifications for Adverse Events

Dose Level	Dose
Recommended dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day[a]

[a] If further dose reduction below 75 mg/day is required, discontinue the treatment.

Table 2. IBRANCE Dose Modification and Management – Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 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. Absolute neutrophil counts (ANC) of $\geq 1000/mm^3$ and platelet counts of $\geq 50{,}000/mm^3$ are recommended to receive IBRANCE.	
CTCAE Grade	**Dose Modifications**

Grade 1 or 2	No dose adjustment is required.
Grade 3[a]	Day 1 of cycle: Withhold IBRANCE, until recovery to Grade ≤2, and 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 the *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 the subsequent cycles.
Grade 3 ANC[b] (<1000 to 500/mm^3) + 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[a]	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose.*

Grading according to CTCAE 4.0 (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).
ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.

[a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

[b] 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. IBRANCE Dose Modification and Management – Non-hematologic Toxicities

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

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

No dose modifications are required on the basis of patient's age, sex, or body weight (see Section 5.2 Pharmacokinetic properties).

Permanently discontinue IBRANCE in patients with severe interstitial lung disease (ILD) or pneumonitis (see Section 4.4 Special warnings and precautions for use).

Special populations

Elderly population: No dose adjustment is necessary in patients ≥65 years of age (see Section 5.2 Pharmacokinetic properties).

Pediatric population: The safety and efficacy of IBRANCE in children and adolescents ≤18 years of age have not been established.

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 on Schedule 3/1 (see Section 5.2 Pharmacokinetic properties).

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥15 mL/min). Insufficient data are available in patients requiring hemodialysis to provide any dosing recommendation in this patient population (see Section 5.2 Pharmacokinetic properties).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

Use of preparations containing St. John's Wort (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4. Special warnings and precautions for use

Myelosuppression

- **Neutropenia**
  Decreased neutrophil counts have been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 (ANC 500 <1000/mm^3) and Grade 4 (ANC <500/mm^3) decreased neutrophil counts were reported.

  In PALOMA-1 and PALOMA-2 the median time to first episode of any grade neutropenia was 15 days (12-700 days) and 28 days (range 12-854) for Grade ≥3 neutropenia. The median duration of Grade ≥3 neutropenia was 33 days (range 1-534).

  In PALOMA-3 the median time to first episode of neutropenia was 15 days (13-317 days) for any grade and 16 days (range 13-587) for Grade ≥3 neutropenia. The median duration for Grade ≥3 neutropenia was 21 days (range 1-167).

An increase in palbociclib exposure has been associated with more severe neutropenia; in Asian subjects, frequency of Grade ≥3 neutropenia is higher than in White subjects (see Section 5.2 Pharmacokinetic properties, Asian race).

Febrile neutropenia has been reported in 1.6% of patients receiving palbociclib in combination with letrozole in PALOMA-2 and in 0.9% of patients receiving palbociclib in combination with fulvestrant in PALOMA-3. One death due to neutropenic sepsis was reported in PALOMA-3.

Febrile neutropenia has not been reported in PALOMA-1. Febrile neutropenia has been reported in about 2% of patients exposed to IBRANCE across the overall clinical program (see Section 4.4 Special warnings and precautions for use - Infections).

Monitor complete blood count 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.

Dosing interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed (see Section 4.2 Posology and method of administration, Table 2).

- **Anaemia**
  Anaemia has been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 and Grade 4 anaemia was observed. In PALOMA-1 and PALOMA-2 the median time to first episode of any grade anaemia was 29 days (range 1-777 days) and 195 days (range 14-760) for Grade ≥3 anaemia. The median duration of Grade ≥3 anaemia was 7 days (range 1-125). In PALOMA-3 the median time to first episode of anaemia was 25 days (12-378 days) for any grade and 52 days (range 15-363) for Grade ≥3 anaemia. The median duration for Grade ≥3 anaemia was 7 days (range 1-125). Across both studies, supportive treatment with red blood cell growth factors and transfusions was administered.

- **Thrombocytopenia**
  Thrombocytopenia has been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 and Grade 4 thrombocytopenia were observed. In PALOMA-1 and PALOMA-2 the median time to first episode of any grade thrombocytopenia was 27 days (range 2-875 days) and 256 days (range 21-652 days) for Grade ≥3 thrombocytopenia. The median duration of Grade ≥3 thrombocytopenia was 7 days (range 1-28 days). In PALOMA-3 the median time to first episode of thrombocytopenia was 15 days (13-422 days) for any grade and 23 days (range

15-57) for Grade ≥3 thrombocytopenia. The median duration for Grade ≥3 thrombocytopenia was 7 days (range 1-9 days).

Interstitial lung disease/pneumonitis

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

Across clinical trials, 1.4% of IBRANCE -treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting (see Section 4.8 Undesirable effects), with fatalities reported.

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 ILD/pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis (see Section 4.2 Posology and method of administration).

Infections

Since IBRANCE has myelosuppressive properties, it may predispose to infections.

Infections have been reported at a higher rate in patients treated with IBRANCE in randomized clinical studies compared to patients treated in the respective comparator arm. Grades 3 and 4 infections occurred in 4.4% and 0.7%, respectively, in patients treated with IBRANCE in either combination compared to patients treated in the respective comparator arms (2.5% and 0%, respectively).

Monitor patients for signs and symptoms of infection and treat as medically appropriate (see Section 4.8 Undesirable effects).

Physicians should inform patients to promptly report any episodes of fever.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with palbociclib. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism, and treated as medically appropriate.

Pre/perimenopausal women

Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered IBRANCE in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

Critical visceral disease

The efficacy and safety of palbociclib have not been studied in patients with critical visceral disease (see Section 5.1 Pharmacodynamic properties).

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 to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose.

Hepatic impairment

Administer IBRANCE with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity (see Section 4.2 Posology and method of administration and Section 5.2 Pharmacokinetic properties).

Renal impairment

Administer IBRANCE with cautions to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity (see Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

Concomitant treatment with inhibitors or inducers of CYP3A4

Strong inhibitors of CYP3A4 may lead to increased toxicity (see Section 4.5 Interaction with other medicinal products and other forms of interaction). Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Coadministration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the IBRANCE dose to 75 mg once daily. When 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 Section 4.5 Interaction with other medicinal products and other forms of interaction).

Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Women of childbearing potential or their partners

Women of childbearing potential or their male partners must use a highly effective method of contraception while taking IBRANCE (see Section 4.6. Fertility, pregnancy and lactation).

4.5. Interaction with other medicinal products and other forms of interaction

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

Agents that may increase palbociclib plasma concentrations

Effect of CYP3A inhibitors

Data from a drug-drug interaction (DDI) study in healthy subjects indicate that coadministration of multiple 200 mg doses of itraconazole with a single 125 mg dose of IBRANCE increased palbociclib total exposure area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and the maximum observed plasma concentration (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125 mg dose of IBRANCE given alone. The concomitant use of strong CYP3A inhibitors including, but not limited to: amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided.

Agents that may decrease palbociclib plasma concentrations

Effect of CYP3A inducers

Data from a DDI study in healthy subjects indicate that coadministration of multiple 600 mg doses of rifampin, a strong CYP3A inducer, with a single 125 mg dose of IBRANCE decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125 mg dose of IBRANCE given alone. Data from a DDI study in healthy subjects 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 dose of IBRANCE given alone.

The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, and St. John's wort, should be avoided.

Coadministration of a moderate CYP3A inducer (modafinil) decreased the plasma exposure of palbociclib in healthy subjects by 32%. Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) can be used concurrently with IBRANCE when unavoidable. No dosing adjustments are required.

Effect of acid reducing agents

Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE tablet under 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 (see Section 4.2 Posology and method of administration).

Effects of IBRANCE on other drugs

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

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.

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.

Letrozole: Data from a clinical study in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 drugs were co-administered.

Fulvestrant: Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the 2 drugs were co-administered.

Goserelin: Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and goserelin when the 2 drugs were co-administered.

Tamoxifen: Data from a DDI study in healthy male subjects indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when palbociclib was given alone.

Drug-drug interaction between palbociclib and oral contraceptives

DDI studies of palbociclib with oral contraceptives have not been conducted (see Section 4.6 Fertility, pregnancy and lactation).

In vitro studies with transporters

Based on *in vitro* data, palbociclib is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of palbociclib with medicinal products that are substrates of palbociclib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g., pravastatin, rosuvastatin, sulfasalazine) may increase their therapeutic effect and adverse reactions.

Based on *in vitro* data, palbociclib may inhibit the uptake transporter organic cationic transporter OCTI and then may increase the exposure of medical product substrates of this transporter (e.g., metformin).

4.6. Fertility, pregnancy and lactation

Fertility

There were no effects on estrous cycle (female rats) or mating and fertility in rats in nonclinical studies. However, no clinical data have been obtained on fertility in human females. Based on male reproductive organ findings (seminiferous tubule degeneration in testis, epididymal hypospermia, lower sperm motility and density, and decreased prostate secretion) in nonclinical safety studies, male fertility may be compromised by treatment with palbociclib (see Section 5.3 Preclinical safety data).

Women of childbearing potential/pregnancy

There are no adequate and well-controlled studies using IBRANCE in pregnant women. Based on findings in animals and mechanism of action, palbociclib can cause fetal harm when administered to a pregnant woman. In animal studies, palbociclib was fetotoxic at maternally-toxic doses. IBRANCE is not recommended during pregnancy and in women of childbearing potential not using contraception.

Females of childbearing potential who are receiving this medicinal product, or their male partners, should use adequate contraceptive methods during therapy and for at least 21 days or 97 days after completing therapy for females and males, respectively.

Lactation

No studies have been conducted in humans to assess the effect of IBRANCE on milk production, its presence in breast milk, or its effects on the breastfed child. It is unknown whether palbociclib is excreted in human milk. Patients receiving palbociclib should not breastfeed.

4.7. Effects on ability to drive and use machines

IBRANCE has minor influence on the ability to drive and use machines. However, patients experiencing fatigue while taking IBRANCE should exercise caution when driving or operating machinery.

4.8. Undesirable effects

Summary of the safety profile

The overall safety profile of IBRANCE is based on pooled data from 872 patients who received palbociclib in combination with endocrine therapy (N=527 in combination with letrozole and N=345 in combination with fulvestrant) in randomised clinical studies in HR-positive, HER2-negative advanced or metastatic breast cancer.

The most common (≥ 20%) adverse reactions of any grade reported in patients receiving palbociclib in randomised clinical studies were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, diarrhoea, alopecia and thrombocytopenia. The most common (≥ 2%) Grade ≥ 3 adverse reactions of palbociclib were neutropenia, leukopenia, infections, anaemia, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased.

Dose reductions or dose modifications due to any adverse reaction occurred in 38.4% of patients receiving IBRANCE in randomised clinical studies regardless of the combination.

Permanent discontinuation due to an adverse reaction occurred in 5.2% of patients receiving IBRANCE in randomised clinical studies regardless of the combination.

Tabulated list of adverse reactions

Table 4 reports the adverse reactions from the pooled dataset of 3 randomised studies. The median duration of palbociclib treatment across the pooled dataset at the time of the final overall survival (OS) analysis was 14.8 months.

Table 5 reports the laboratory abnormalities observed in pooled datasets from 3 randomised studies.

The adverse reactions are listed by system organ class and frequency category. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to

< 1/10), and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse reactions based on pooled dataset from 3 randomised studies (N=872) and during post-marketing experience

System organ class **Frequency** **Preferred term[a] (PT)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Infections and infestations			
Very common			
Infections[b]	516 (59.2)	49 (5.6)	8 (0.9)
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	716 (82.1)	500 (57.3)	97 (11.1)
Leukopenia[d]	424 (48.6)	254 (29.1)	7 (0.8)
Anaemia[e]	258 (29.6)	45 (5.2)	2 (0.2)
Thrombocytopenia[f]	194 (22.2)	16 (1.8)	4 (0.5)
Common			
Febrile neutropenia	12 (1.4)	10 (1.1)	2 (0.2)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	152 (17.4)	8 (0.9)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	79 (9.1)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	48 (5.5)	1 (0.1)	0 (0.0)
Lacrimation increased	59 (6.8)	0 (0.0)	0 (0.0)
Dry eye	36 (4.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders			
Common			
Epistaxis	77 (8.8)	0 (0.0)	0 (0.0)
ILD/pneumonitis[i]	12 (1.4)	1 (0.1)	0 (0.0)
Gastrointestinal disorders			
Very common			
Stomatitis[g]	264 (30.3)	8 (0.9)	0 (0.0)
Nausea	314 (36.0)	5 (0.6)	0 (0.0)
Diarrhoea	238 (27.3)	9 (1.0)	0 (0.0)
Vomiting	165 (18.9)	6 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	158 (18.1)	7 (0.8)	0 (0.0)
Alopecia	234 (26.8)	N/A	N/A
Dry skin	93 (10.7)	0 (0.0)	0 (0.0)
Common			

Table 4. Adverse reactions based on pooled dataset from 3 randomised studies (N=872) and during post-marketing experience

System organ class **Frequency** **Preferred term[a] (PT)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Palmar-plantar erythrodysaesthesia syndrome	16 (1.8)	0 (0.0)	0 (0.0)
Uncommon			
Erythema multiforme	1 (0.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	362 (41.5)	23 (2.6)	2 (0.2)
Asthenia	118 (13.5)	14 (1.6)	1 (0.1)
Pyrexia	115 (13.2)	1 (0.1)	0 (0.0)
Investigations			
Very common			
ALT increased	92 (10.6)	18 (2.1)	1 (0.1)
AST Increased	99 (11.4)	25 (2.9)	0 (0.0)
Common			
Blood creatinine increased	57 (6.5)	3 (0.3)	2 (0.2)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease; N/n=number of patients; N/A=not applicable.

[a] PTs are listed according to MedDRA 17.1.

[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.

[c] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

[d] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.

[e] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.

[f] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.

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

[h] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

[i] ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial Lung Disease (narrow).

Table 5. Laboratory abnormalities observed in pooled dataset from 3 randomised studies (N=872)

	IBRANCE plus letrozole or fulvestrant			**Comparator arms***		
Laboratory abnormalities	**All grades %**	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
WBC decreased	97.4	41.8	1.0	26.2	0.2	0.2
Neutrophils decreased	95.6	57.5	11.7	17.0	0.9	0.6

Blood creatinine increased	95.5	1.6	0.3	86.8	0.0	0.0
Anaemia	80.1	5.6	N/A	42.1	2.3	N/A
Platelets decreased	65.2	1.8	0.5	13.2	0.2	0.0
AST increased	55.5	3.9	0.0	43.3	2.1	0.0
ALT increased	46.1	2.5	0.1	33.2	0.4	0.0

WBC=white blood cells; AST=aspartate aminotransferase; ALT=alanine aminotransferase; N=number of patients; N/A=not applicable.
Note: Laboratory results are graded according to the NCI CTCAE version 4.0 severity grade.
* letrozole or fulvestrant

Description of selected adverse reactions

Overall, neutropenia of any grade was reported in 716 (82.1%) patients receiving IBRANCE regardless of the combination, with Grade 3 neutropenia being reported in 500 (57.3%) patients, and Grade 4 neutropenia being reported in 97 (11.1%) patients (see Table 4).

The median time to first episode of any grade neutropenia was 15 days (12-700 days) and the median duration of Grade ≥ 3 neutropenia was 7 days across 3 randomised clinical studies.

Febrile neutropenia has been reported in 0.9% of patients receiving IBRANCE in combination with fulvestrant and in 1.7% of patients receiving palbociclib in combination with letrozole.

Febrile neutropenia has been reported in about 2% of patients exposed to IBRANCE across the overall clinical programme.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor lmpor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
JI. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext .1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

4.9. Overdose

In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and haematological (e.g., neutropenia) toxicity may occur. There is no known antidote for palbociclib. The treatment of IBRANCE overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Palbociclib is a highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation.

Pharmacodynamic effects

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high efficacy against luminal breast cancers, particularly estrogen receptor (ER)-positive breast cancers. In the cell lines tested, the loss of retinoblastoma (Rb) was associated with loss of palbociclib activity. Available clinical data are reported in the clinical efficacy and safety section (see Section 5.1 Pharmacodynamic properties). Mechanistic analyses revealed that the combination of palbociclib with anti-estrogen agents enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signaling and growth arrest. *In vivo* studies using a patient-derived ER-positive breast cancer xenograft model (HBCx-34) demonstrated that the combination of palbociclib and letrozole further enhanced inhibition of Rb phosphorylation, downstream signaling, and dose-dependent tumor growth. Studies are ongoing investigating the importance of Rb expression for the activity of palbociclib in fresh tumor samples.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched electrocardiogram (ECG) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with advanced breast cancer. Palbociclib did not prolong the QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

Clinical trial efficacy

Study 1:

The efficacy of palbociclib was evaluated in a randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer.

The study was comprised of a limited Phase 1 portion (N=12), designed to confirm the safety and tolerability of the combination palbociclib plus letrozole, followed by a randomized Phase 2 portion (N = 165), designed to evaluate the efficacy and safety of palbociclib in combination with letrozole compared with letrozole alone in the first-line treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer.

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).

The patient demographic and baseline characteristics were generally balanced between the study arms in terms of age, race, disease sites, stage, and prior therapies.

The primary endpoint of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

The median PFS (mPFS) for patients in the palbociclib plus letrozole arm was 20.2 months (95% confidence interval [CI]: 13.8, 27.5) and 10.2 months (95% CI: 5.7, 12.6) for patients in the letrozole-alone arm. The observed hazard ratio (HR) was 0.488 (95% CI: 0.319, 0.748) in favor of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of 0.0004.

At the final overall survival (OS) analysis, the observed HR was 0.897 (95% CI: 0.623, 1.294) with a stratified 1-sided p-value of 0.2812. The median OS in the palbociclib plus letrozole arm was 37.5 months (95% CI: 31.4, 47.8) and in the letrozole alone arm was 34.5 months (95% CI: 27.4, 42.6).

The estimated survival probabilities at 12, 24, and 36 months between the 2 treatment arms were 89.0% versus 87.0%, 77.9% versus 71.1%, and 50.8% versus 47.4%, in favor of palbociclib plus letrozole, respectively.

Study 2:

The efficacy of palbociclib in combination with letrozole versus letrozole plus placebo was evaluated in an international, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in women with ER-positive,

HER2-negative locally advanced or metastatic breast cancer (PALOMA-2) who had not received prior systemic treatment for their advanced disease.

A total of 666 postmenopausal women were randomized 2:1 to either the palbociclib plus letrozole arm or to the placebo plus letrozole arm and were stratified by site of disease (visceral, non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (*de novo* metastatic, ≤12 months from the end of adjuvant treatment to disease recurrence, >12 months from the end of adjuvant treatment to disease recurrence), and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy, no prior hormonal therapy). Patients with advanced symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

Patients continued to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Patients were well matched for baseline demographics and disease characteristics between the palbociclib plus letrozole arm and the placebo plus letrozole arm. The median age of patients enrolled in this study was 62 years (range 28-89); 48.3% of patients had received chemotherapy and 56.3% had received antihormonal therapy in the (neo)adjuvant setting prior to their diagnosis of advanced breast cancer, while 37.2% of patients had received no prior systemic therapy in the (neo)adjuvant setting. Most patients (97.4%) had metastatic disease at baseline; 22.7% of patients had bone only disease and 49.2% of patients had visceral disease.

The primary endpoint of the study was PFS evaluated according to RECIST version 1.1 as assessed by investigator. Secondary efficacy endpoints included objective response (OR), duration of response (DOR), clinical benefit response (CBR), overall survival (OS), safety, EQ-5D scores and health-related quality of life (QoL) assessed using the FACT-B questionnaire.

At the data cutoff date of 26 February 2016, the study met its primary objective of improving PFS. The observed HR was 0.576 (95% CI: 0.463, 0.718) in favor of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of <0.000001. An updated analysis of the primary and secondary endpoints was performed after additional 15 months of follow up (data cutoff date: 31 May 2017). A total of 405 PFS events were observed; 245 events (55.2%) in the palbociclib plus letrozole arm and 160 (72.1%) in the comparator arm respectively.

Table 6 shows the efficacy results based on the primary and the updated analyses from the PALOMA-2 study, as assessed by the investigator and by the independent review.

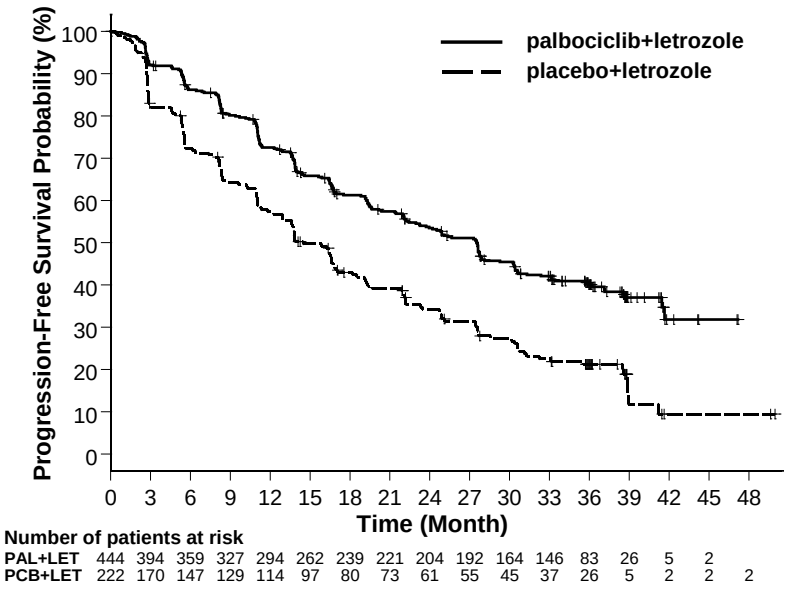
Table 6. PALOMA-2 (Intent-to-Treat Population) - Efficacy Results Based on Primary and Updated Cutoff Dates

	Primary Analysis (26 February 2016 Cutoff)		Updated Analysis (31 May 2017 Cutoff)	
	IBRANCE plus Letrozole (N = 444)	**Placebo plus Letrozole (N = 222)**	**IBRANCE plus Letrozole (N = 444)**	**Placebo plus Letrozole (N = 222)**
Progression-free Survival by Investigator Assessment				
Number of events (%)	194 (43.7)	137 (61.7)	245 (55.2)	160 (72.1)
Median PFS [months (95% CI)]	24.8 (22.1, NE)	14.5 (12.9, 17.1)	27.6 (22.4 30.3)	14.5 (12.3, 17.1)
Hazard ratio [(95% CI) and p-value]	0.576 (0.463, 0.718), p<0.000001		0.563 (0.461, 0.687), p<0.000001	
Progression-free Survival by Independent Assessment				
Number of events (%)	152 (34.2)	96 (43.2)	193 (43.5)	118 (53.2)
Median PFS [months (95% CI)] and p-value	30.5 (27.4, NE)	19.3 (16.4, 30.6)	35.7 (27.7, 38.9)	19.5 (16.6, 26.6)
Hazard ratio (95% CI) and 1-sided p-value	0.653 (0.505, 0.844), p=0.000532		0.611 (0.485, 0.769), p=0.000012	
OR* [% (95% CI)]	46.4 (41.7, 51.2)	38.3 (31.9, 45.0)	47.5 (42.8, 52.3)	38.7 (32.3, 45.5)
OR* measurable disease [% (95% CI)]	60.7 (55.2, 65.9)	49.1 (41.4, 56.9)	62.4 (57.0, 67.6)	49.7 (42.0, 57.4)
DOR* [months (95% CI)]	20.1 (19.3, 28.0)	16.7 (13.8, 22.5)	25.3 (22.1, 34.5)	16.8 (14.2, 25.3)
CBR* [% (95% CI)]	85.8 (82.2, 88.9)	71.2 (64.7, 77.0)	85.6 (82.0, 88.7)	71.2 (64.7, 77.0)

N=number of patients; CI=confidence interval; NE=not estimable; OR=objective response; CBR=clinical benefit response; DOR=duration of response; PFS=progression-free-survival.
Secondary endpoints results are based on confirmed and unconfirmed responses according to RECIST 1.1.

The Kaplan-Meier curves for PFS based on the updated cutoff date of 31 May 2017 are displayed in Figure 1 below.

Figure 1. Kaplan-Meier Plot of Progression-free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-2 Study (31 May 2017)



Abbreviations: LET=letrozole; PAL=palbociclib; PCB=placebo.

A series of prespecified subgroup PFS analyses was performed based on baseline demographic and disease characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in the palbociclib plus letrozole arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics in the primary and in the updated analyses.

At the time of the updated analyses, the times to initiation of the first and the second subsequent anticancer therapies were also assessed. Similarly, the time to initiation of subsequent chemotherapy was also evaluated. The results from these analyses are shown in Table 7.

Table 7. PALOMA-2 Study: Time to Initiation of Subsequent Anticancer Therapies (31-May-2017 Cutoff Date)

	IBRANCE plus letrozole (N=444)	Placebo plus letrozole (N=222)
Median (95% CI) time to first subsequent therapy	28.0 (23.6, 29.6)	17.7 (14.3, 21.5)
Median (95% CI) time to second subsequent therapy	38.8 (34.4, NE)	28.8 (25.7, 33.5)
Median (95% CI) time to first chemotherapy	40.4 (34.7, 47.3)	29.9 (25.6, 35.1)

N=number of patients; CI=confidence interval

Patients with advanced, symptomatic visceral spread at risk of life-threatening complications in the short term were not included in PALOMA-2. Objective Response Rate (ORR) was higher in patients with visceral disease treated with palbociclib plus letrozole compared to placebo plus letrozole (58.9% [95% CI: 52.0, 65.5], versus 45.5% [95% CI: 35.9, 55.2], respectively), while in patients with non visceral metastases (n= 342, of whom 151 had bone only disease) ORR was comparable between treatment groups (34.8% [95% CI: 28.6, 41.3], versus 31.3% [95% CI: 22.8, 40.7]) The overall survival (OS) data were not mature at the time of the final PFS analysis (20% of patients had died). Patients will continue to be followed for the final analysis.

An analysis of time-to-deterioration composite endpoint (TTD) in Functional Assessment of Cancer Therapy-Breast (FACT-B), defined as the time between baseline and first occurrence of decrease of ≥7 points in FACT-B scores, was carried out based on survival analysis methods using a Cox proportional hazards model and log-rank test. No statistically significant difference was observed in TTD in FACT-B total scores between the palbociclib plus letrozole arm and the placebo plus letrozole arm (HR of 1.042 [95% CI: 0.838, 1.295]; 1-sided p-value=0.663).

The results from the final OS analysis from the PALOMA-2 study are presented in Table 8. After a median follow-up time of 90 months, the final OS results were not statistically significant. The Kaplan-Meier plot of OS is shown in Figure 2.

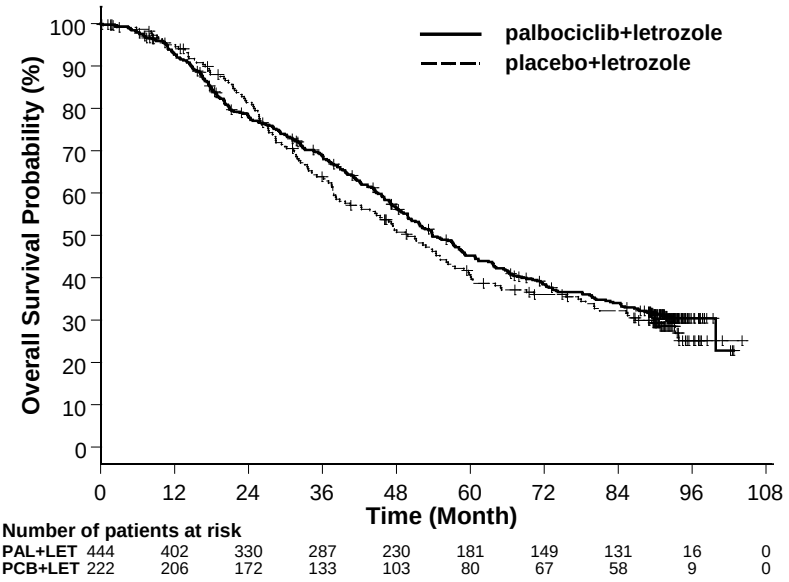
Table 8. PALOMA-2 (Intent-to-Treat Population) – Final Overall Survival Results

Final Overall Survival (OS) (15 November 2021 Cutoff)		
	IBRANCE plus letrozole (N = 444)	**Placebo plus letrozole (N = 222)**
Number of OS events (%)	287 (64.6)	148 (66.7)
Number of subjects remaining in follow-up (%)	116 (26.1)	48 (21.6)
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.
[*] Not statistically significant.
[†] 1-sided p-value from the log-rank test stratified by disease site (visceral vs. non-visceral) per randomization.

Figure 2. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-2



Study 3: Randomized, Phase 3 study of IBRANCE in combination with fulvestrant (PALOMA-3)

The efficacy of palbociclib in combination with fulvestrant versus placebo plus fulvestrant was evaluated in an international, randomized, double-blind, parallel-group, multicenter study conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy.

A total of 521 pre/postmenopausal women whose disease had progressed during or within 12 months after completion of adjuvant endocrine therapy or during or within 1 month after prior endocrine therapy for advanced disease were randomized 2:1 to the palbociclib plus fulvestrant arm or the placebo plus fulvestrant arm and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases.

Crossover between treatment arms was not allowed.

Patients were balanced for baseline demographics and prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. The majority of patients in each treatment arm were White, <65 years of age, had documented sensitivity to prior hormonal therapy, and were postmenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen. More than a half had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, had visceral metastases, and had received more than 1 prior hormonal regimen for the primary diagnosis.

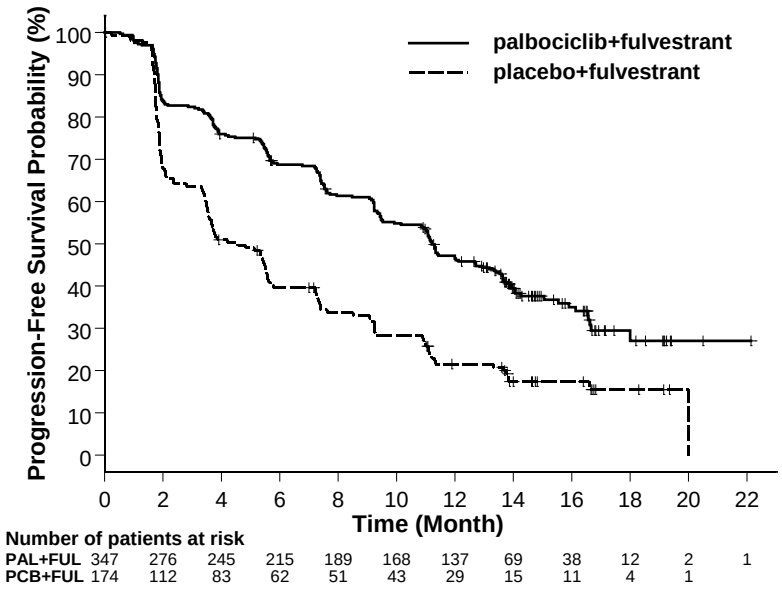
The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST version 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, DOR, CBR, OS, safety, change in QoL, and TTD. Patient-reported outcomes including Global QoL and pain were measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Breast Cancer Module (BR23) questionnaire.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events at final analysis; the results crossed the prespecified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect.

The estimated HR from the stratified analysis was 0.422 (95% CI: 0.318, 0.560; 1-sided p<0.000001) in favor of palbociclib plus fulvestrant.

The mPFS was 9.2 months (95% CI: 7.5, NE) in the palbociclib plus fulvestrant arm and 3.8 months (95% CI: 3.5, 5.5) in the placebo plus fulvestrant arm.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3 (23 October 2015 Cutoff)



CI=confidence interval; FUL=fulvestrant; N=number of patients; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Table 9. Efficacy Results – Study 3 (Investigator Assessment, Intent-to-Treat Population)

	Final Analysis (05-Dec-2014 Cutoff)		Updated Analysis (23-Oct-2015 Cutoff)	
	IBRANCE plus Fulvestrant (N = 347)	**Placebo plus Fulvestrant (N = 174)**	**IBRANCE plus Fulvestrant (N = 347)**	**Placebo plus Fulvestrant (N = 174)**
Progression-Free Survival				
Median PFS [months (95% CI)]	9.2 (7.5, NE)	3.8 (3.5, 5.5)	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio [(95% CI) and p-value]	0.422 (0.318, 0.560), p<0.000001		0.497 (0.398, 0.620), p<0.000001	
ORR [% (95% CI)]	20.2 (16.1, 24.1)	11.5 (7.2, 17.2)	26.2 (21.7, 31.2)	13.8 (9.0, 19.8)
ORR measurable disease [% (95% CI)]	26.1 (21.0, 31.8)	14.5 (9.1, 21.5)	33.7 (28.1, 39.7)	17.4 (11.5, 24.8)
DOR [months (95% CI)]	9.3 (4.0, NE)	5.7 (3.7, 5.7)	9.2 (7.2, 10.4)	7.4 (3.9, NE)
CBRR [% (95% CI)]	41.5 (36.3, 46.9)	21.8 (15.9, 28.7)	68.0 (62.8, 72.9)	39.7 (32.3, 47.3)

CBRR=clinical benefit response rate; CI=confidence interval; DOR=duration of response; N=number of patients; NE=not estimable; PFS=progression-free survival; ORR=objective response rate.

Prolongation of PFS in the palbociclib plus fulvestrant arm was also demonstrated in individual patient subgroups supporting internal consistency of PFS benefit findings within the study, and was supported by a random sample Blinded Independent Central Review (BICR) audit analysis conducted on 40.5% (N=211) of 521 randomized patients.

Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior and for duration of Study 2.

The palbociclib plus fulvestrant arm demonstrated similar clinical benefit in the pre/perimenopausal patient population (HR = 0.435 [95% CI: 0.228, 0.831]) and postmenopausal population (HR= 0.409 [95% CI: 0.298, 0.560]). Similarly, the mPFS for the palbociclib plus fulvestrant arm was 9.5 months (95% CI: 7.2, NE) in the pre/perimenopausal setting versus 9.2 months (95% CI: 7.5, NE) in the postmenopausal setting; while the mPFS in the placebo plus fulvestrant arm was 5.6 months (95% CI: 1.8, NE) in the pre/perimenopausal setting versus 3.7 months (95% CI: 3.5, 5.5) in the postmenopausal setting.

Patient-reported symptoms were assessed using the EORTC QLQ-C30 and EORTC QLQ-BR23. A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the placebo plus fulvestrant arm completed the questionnaire at baseline and at least 1 postbaseline visit.

Results of the Global Health Status/QoL comparison between the palbociclib plus fulvestrant arm versus the fulvestrant plus placebo arm showed a statistically significant difference favoring the palbociclib plus fulvestrant arm compared to the placebo plus fulvestrant arm (-0.9 [95% CI: -2.5, 0.7] versus -4.0 [95% CI: -6.3, -1.7], respectively; 2-sided p=0.0313). In addition, a comparison in emotional functioning also showed a statistically significant difference favoring the palbociclib plus fulvestrant arm compared to the placebo plus fulvestrant arm (2.7 [95% CI: 1.1, 4.3] versus-1.9 [95% CI: -4.2, 0.5], respectively; 2-sided p=0.0016) (data unadjusted for multiple comparisons).

Time to Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).

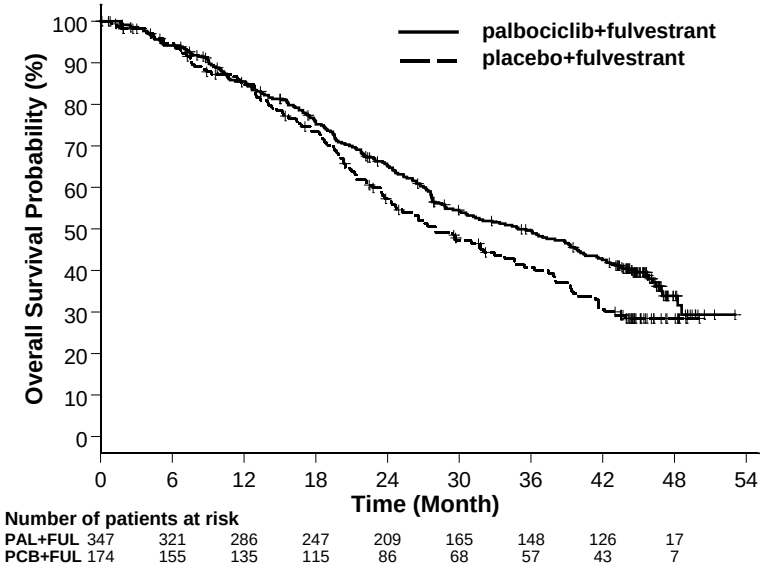
After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (59.5% of randomized patients). A clinically meaningful 6.9-month improvement in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed, although this result was not statistically significant at the prespecified significance level of 0.0235. A higher proportion of patients in the placebo plus fulvestrant arm received post-progression systemic treatments overall in comparison with the patients in the palbociclib plus fulvestrant arm (80.5% versus 71.8%) respectively. Also, in placebo plus fulvestrant arm, 15.5% of randomized patients received palbociclib and other CDK inhibitors as post progression subsequent treatments. The results from the final OS data from PALOMA-3 Study are presented in Table 10. The relevant Kaplan-Meier plots are shown in Figures 3 and 4.

Table 10. Efficacy Results – Study 3 (Investigator Assessment, Intent-to-Treat Population)

Final Overall Survival (OS) (13 April 2018 Cutoff)		
	IBRANCE plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	201 (57.9)	109 (62.6)
Median (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=0.0429[†*]	

CI=confidence interval.
[*] Not statistically significant.
[†] 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomization.

Figure 4. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-3



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

A positive treatment effect of palbociclib plus fulvestrant versus placebo plus fulvestrant on OS was observed in the majority of the prespecified subgroups. Due to the low event number and smaller sample size in some of the prespecified subgroups, the magnitude of estimated effect of palbociclib added to fulvestrant could not always be determined. The OS results from patients' subgroups defined by stratification factors at randomization are reported in Table 11 below.

Table 11. Overall Survival in Patients Subgroups Defined by Stratification Factors

	PAL + FUL	PCB + FUL	HR (95% CI)	p-value*
ITT Sub-group	**ne/N**	**ne/N**		
Menopausal Status at Study Entry				
Postmenopausal	161/275	91/138	0.73 (0.57, 0.95)	p=0.009
Peri/premenopausal	40/72	18/36	1.07 (0.61, 1.86)	p=0.41
Documented Sensitivity to Prior Hormonal Therapy				
Yes	150/274	84/136	0.72 (0.55, 0.94)	p=0.008
No	51/73	25/38	1.14 (0.70, 1.84)	p=0.297
Site of Metastatic Disease				
Visceral	138/206	72/105	0.85 (0.64, 1.13)	p=0.132
Non-visceral	63/141	37/69	0.69 (0.46, 1.04)	p=0.036

CI=confidence interval; FUL=fulvestrant; HR=Hazard Ratio; ITT=Intent-to-Treat; ne=number of events; N=number of patients; PAL=palbociclib; PCB=placebo.

* One sided p-value. No multiplicity adjustments were made for the subgroup analyses.

The estimated survival probabilities for palbociclib plus fulvestrant versus placebo plus fulvestrant were respectively: 65.3% (95% CI: 59.9, 70.2) vs. 57.3% (95% CI: 49.2, 64.6) at 2 years and 49.6% (95% CI: 44.0, 54.9) vs. 40.8% (95% CI: 32.9, 48.5) at 3 years.

5.2. Pharmacokinetic properties

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

Absorption

The T_{max} of palbociclib is generally observed between 4 to 12 hours following oral administration of IBRANCE tablets. The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increase proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulates with a median accumulation ratio of 2.4 (range 1.5-4.2).

Food effect: The 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. Based on these results, IBRANCE tablets may be taken with or without food.

Gastric pH elevating medication effect: Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE tablet under 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.

Distribution

Binding of palbociclib to human plasma proteins *in vitro* was ~85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The 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 (26%) L.

Metabolism

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

Elimination

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

Age, gender, and body weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging 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 palbociclib have not been evaluated in patients ≤18 years of age.

Elderly population

Of 444 patients who received IBRANCE in Study A5481008 (PALOMA-2), 181 patients (41%) were ≥65 years of age with 133 (30%) patients between the age of 65 and 74, and 48 (11%) patients ≥75 years of age. Of 347 patients who received IBRANCE in Study A5481023 (PALOMA-3), 86 patients (25%) were ≥65 years of age with 59 (17%) patients between the age of 65 and 74, and 27 (8%) patients ≥75 years of age. No overall differences in safety were observed across all age groups and elderly age groups. Neutropenia was the most common adverse event with palbociclib across all age groups; however, the incidence of febrile neutropenia was low in all age groups.

Hepatic impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic function indicate that 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 hepatic impairment (Child-Pugh class C), respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) was 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 with advanced cancer where 40 patients had mild hepatic impairment based on National Cancer institute (NCI) classification (total bilirubin ≤Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the pharmacokinetics (PK) of palbociclib.

Renal impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal function indicate that total palbociclib exposure (AUC_{inf}) was 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 (CrCl ≥90 mL/min) renal function. Peak palbociclib exposure (C_{max}) was 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 with advanced cancer where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the PK of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

Asian race

In a pharmacokinetic study in healthy volunteers, palbociclib AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects compared with non-Asian subjects after a single oral dose. However, this finding was not reproduced consistently in subsequent studies in Japanese or Asian breast cancer patients after multiple dosing. Based on an analysis of the cumulative pharmacokinetic, safety, and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary.

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

did not prolong QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

5.3. Preclinical safety data

The primary target organ findings following single and/or repeat dosing included hematolymphopoietic and male reproductive organ effects in rats and dogs, and effects on bone and actively growing incisors in rats only. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. Partial to full reversal of effects on the hematolymphopoietic, male reproductive systems, and incisor teeth were established, whereas the bone effect was not reversed following a 12-week non-dosing period. In addition, cardiovascular effects (QTc prolongation, decreased heart rate, and increased RR interval and systolic blood pressure) were identified in telemetered dogs at ≥4 times human clinical exposure based on C_{max}.

Carcinogenicity

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell tumors in the central nervous system of males at 30 mg/kg/day; there were no neoplastic findings in female rats at any dose up to 200 mg/kg/day. The NOEL for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times the human clinical exposure based on AUC) and 200 mg/kg/day (approximately 4 times the human clinical exposure based on AUC) in males and females, respectively. The relevance of the male rat neoplastic finding to humans is unknown.

Genotoxicity

Palbociclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the *in vitro* human lymphocyte chromosome aberration assay.

Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells *in vitro* and in the bone marrow of male rats at doses ≥100 mg/kg/day. The no-observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

Impairment of fertility

Palbociclib did not affect mating or fertility in female rats at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC) and no adverse effects were observed in female reproductive tissues in repeat-dose toxicity

studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 5 and 3 times human clinical exposure based on AUC, respectively).

Palbociclib is considered to have the potential to impair reproductive function and fertility in male humans based on nonclinical findings in rats and dogs. Palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, and decreased secretion. These findings were observed in rats and/or dogs at exposures ≥9 times or subtherapeutic compared to human clinical exposure based on AUC. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. Despite these male reproductive organ findings, there were no effects on mating or fertility in male rats at projected exposure levels 13 times human clinical exposure based on AUC.

Developmental toxicity

Palbociclib was fetotoxic in pregnant animals. An increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra) at ≥100 mg/kg/day was observed in rats. Reduced fetal body weights were observed at a maternally toxic dose of 300 mg/kg/day in rats (3 times human clinical exposure based on AUC), and an increased incidence of skeletal variations, including small phalanges in the forelimb was observed at a maternally toxic dose of 20 mg/kg/day in rabbits (4 times human clinical exposure based on AUC). Actual fetal exposure and cross-placenta transfer have not been examined.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core
Microcrystalline cellulose, colloidal silicon dioxide, crospovidone, magnesium stearate, and succinic acid.

Film coating
Hypromellose, titanium dioxide, triacetin, indigo carmine aluminum lake, iron oxide red (75 mg and 125 mg tablets only), and iron oxide yellow (100 mg tablets only).

6.2. Special precautions for storage

Store below 30°C.

6.3. Special precautions for disposal and other handling

Store in the original blister package in order to protect from moisture.

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

7. MARKETING AUTHORISATION HOLDER NAME AND ADDRESS

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Freiburg Im Breisgau
Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER

Ibrance 75 mg Film-coated tablet; Box of 1 blister @ 7 film-coated tablets; No. Reg. DKI2158501617A1
Ibrance 100 mg Film-coated tablet; Box of 1 blister @ 7 film-coated tablets; No. Reg. DKI2158501617B1
Ibrance 125 mg Film-coated tablet; Box of 1 blister @ 7 film-coated tablets; No. Reg. DKI2158501617C1

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

02/2025

CDS version 19.0

Nama Generik: Palbociclib
Nama Dagang: Ibrance
Tanggal Efektif CDS: 29 Juli 2024
Menggantikan: 16 Februari 2024
Disetujui oleh BPOM:

Brosur kemasan: Informasi bagi pengguna

IBRANCE 75 mg tablet salut selaput
IBRANCE 100 mg tablet salut selaput
IBRANCE 125 mg tablet salut selaput
Palbociclib

Bacalah brosur ini dengan cermat sebelum Anda menggunakan obat ini karena mengandung informasi yang penting untuk Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum di dalam brosur ini. Lihat bagian 8.

Isi brosur ini:

1. Nama produk
IBRANCE®

2. Keterangan produk
IBRANCE 75 mg tablet tersedia dalam bentuk tablet salut selaput bundar berwarna ungu muda dengan cap “Pfizer” pada satu sisi dan “PBC 75” pada sisi sebaliknya.

IBRANCE 100 mg tablet tersedia dalam bentuk tablet salut selaput oval berwarna hijau dengan cap “Pfizer” pada satu sisi dan “PBC 100” pada sisi sebaliknya.

IBRANCE 125 mg tablet tersedia dalam bentuk tablet salut selaput oval berwarna ungu muda dengan cap “Pfizer” pada satu sisi dan “PBC 125” pada sisi sebaliknya.

IBRANCE 75 mg, 100 mg, dan 125 mg tersedia dalam kemasan blister berisi 7 tablet di dalam dus.

3. Apa kandungan obat ini?
Masing-masing tablet salut selaput mengandung palbociclib bentuk basa 75 mg, 100 mg, atau 125 mg.

Bahan lainnya adalah:
Inti tablet
Mikrokristalin selulosa, silikon dioksida koloidal, krospovidon, magnesium stearat, dan asam suksinat.

Lapisan selaput
Hipromelosa, titanium oksida, triasetin, indigo karmin aluminum lake, merah besi oksida (khusus tablet 75 mg dan 125 mg), dan kuning besi oksida (khusus tablet 100 mg).

4. Kekuatan obat
75 mg, 100 mg, atau 125 mg

5. Apa kegunaan obat ini?
IBRANCE adalah obat antikanker yang mengandung bahan aktif palbociclib.

Palbociclib bekerja dengan menghambat protein yang disebut cyclin-dependent kinase 4 dan 6 yang mengatur pertumbuhan dan pembelahan sel. Penghambatan protein ini dapat memperlambat pertumbuhan kanker dan menunda progresi kanker yang Anda derita.

IBRANCE digunakan untuk mengobati pasien dengan jenis kanker payudara tertentu (positif reseptor hormon, negatif reseptor faktor pertumbuhan epidermal manusia 2) yang telah menyebar keluar dari tumor asal dan/atau ke organ lain. Obat ini diberikan bersamaan dengan letrozol atau fulvestran, yang digunakan sebagai terapi antikanker hormonal.

Pada wanita pramenopause atau sekitar menopause, terapi endokrin harus dikombinasikan dengan agonis hormon pelepasan hormon peluteinan (LHRH).

Jika Anda memiliki pertanyaan tentang cara kerja IBRANCE atau mengapa obat ini diresepkan kepada Anda, tanyakan kepada dokter Anda.

6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini?
Selalu minum obat ini dengan tepat sesuai anjuran dokter atau apoteker Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

Dosis yang disarankan adalah 125 mg IBRANCE sekali sehari selama 3 minggu diikuti dengan 1 minggu tanpa IBRANCE. Dokter Anda akan memberi tahu jumlah tablet IBRANCE yang harus diminum.

Jika Anda mengalami efek samping tertentu saat meminum IBRANCE (lihat bagian “8. Efek yang tidak diinginkan”), dokter Anda dapat menurunkan dosis atau menghentikan pengobatan, baik sementara atau permanen. Dosis mungkin diturunkan ke salah satu dari kekuatan dosis lainnya yang tersedia, 100 mg atau 75 mg.

Minum IBRANCE sekali sehari pada waktu yang sama setiap hari sebelum atau sesudah makan.

Telan tablet utuh dengan segelas air. Jangan mengunyah atau menghancurkan tablet. Jangan membelah tablet sebelum ditelan. Jangan diminum jika tablet pecah, retak, atau tidak utuh.

Jika Anda berhenti meminum IBRANCE

Jangan berhenti meminum IBRANCE kecuali atas perintah dokter.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

7. Kapan seharusnya Anda tidak menggunakan obat ini?
Jangan meminum IBRANCE:

- Jika Anda alergi terhadap palbociclib atau bahan lain dalam obat ini (Dicantumkan di bagian 3).
- Penggunaan sediaan yang mengandung St. John's Wort, yaitu produk herbal yang digunakan untuk mengobati depresi dan kecemasan ringan, harus dihindari saat Anda mengonsumsi IBRANCE.

Kehamilan dan menyusui
Anda tidak boleh menggunakan IBRANCE jika sedang hamil.

Anda tidak boleh hamil selama meminum IBRANCE.

Diskusikan penggunaan alat kontrasepsi dengan dokter jika ada kemungkinan bahwa Anda atau pasangan Anda bisa hamil.

Jika Anda hamil atau sedang menyusui, merasa mungkin sedang hamil, atau berencana memiliki bayi, mintalah saran dokter atau apoteker sebelum meminum obat ini.

Wanita usia subur yang menerima produk obat ini, atau pasangan prianya harus memakai metode kontrasepsi yang memadai (misalnya memakai dua jenis kontrasepsi seperti kondom dan diafragma). Kedua metode ini harus digunakan selama terapi dan sekurang-kurangnya 3 minggu setelah menyelesaikan terapi bagi wanita dan sekurang-kurangnya 14 minggu untuk pria.

<u>Menyusui</u>
Anda dilarang menyusui selama meminum IBRANCE. Tidak diketahui apakah IBRANCE diekskresikan pada ASI.

<u>Kesuburan</u>
Palbociclib dapat menurunkan kesuburan pada pria. Oleh karena itu, pria dapat mempertimbangkan pengawetan sperma sebelum mengonsumsi IBRANCE.

<u>Pasien anak-anak dan remaja</u>
IBRANCE tidak boleh diberikan pada anak-anak atau remaja (usia 18 tahun atau kurang).

Mengemudi dan menjalankan mesin
Efek samping yang sangat umum adalah rasa letih. Jika Anda merasakan keletihan yang tidak biasa, berhati-hatilah saat mengemudi atau mengoperasikan mesin.

8. Efek yang tidak diharapkan
Sebagaimana kebanyakan obat, obat ini bisa mengakibatkan efek samping, meski tidak dirasakan semua orang.

Hubungi dokter Anda segera jika mengalami gejala-gejala berikut:

- demam, menggigil, lemas, sesak napas, perdarahan, atau mudah lebam yang bisa jadi merupakan tanda kelainan darah yang serius.
- kesulitan bernapas, batuk kering, atau nyeri dada yang bisa jadi merupakan tanda adanya peradangan paru-paru.

Efek samping lain dari IBRANCE dapat meliputi:

Efek samping yang sangat umum (dapat dialami lebih dari 1 di antara 10 orang):
- Infeksi
- Penurunan sel darah putih, sel darah merah, dan trombosit
- Merasakan kelelahan
- Penurunan nafsu makan
- Peradangan mulut dan bibir (stomatitis), mual, muntah, diare
- Ruam
- Kerontokan rambut
- Lemah
- Demam
- Hasil tes darah untuk organ hati tidak normal
- Kulit kering

Efek samping yang umum (dapat dialami hingga 1 di antara 10 orang):
- Demam disertai penurunan jumlah sel darah putih (demam neutropenia)
- Penglihatan kabur, peningkatan pengeluaran air mata, mata kering
- Perubahan indra perasa (disgeusia)
- Mimisan
- Telapak tangan dan/atau telapak kaki memerah, nyeri, mengelupas, membengkak, dan melepuh (Sindrom Eritrodisestesia Palmar Plantar [PPES])
- Hasil tes darah untuk ginjal tidak normal (kadar kreatinin tinggi dalam darah)

Efek samping yang tidak umum (dapat dialami oleh maksimal 1 di antara 100 orang):
- Reaksi kulit yang menyebabkan bintik atau noda merah pada kulit yang mungkin terlihat seperti target atau “sasaran tembak” dengan bagian tengah berwarna merah tua yang dikelilingi oleh cincin merah yang berwarna lebih muda (eritema multiforme).

Ini tidak mencakup semua kemungkinan efek samping IBRANCE.

Hubungi dokter Anda untuk mendapatkan saran medis terkait efek samping.

Melaporkan efek samping
Jika Anda mendapatkan efek samping diatas, hubungi dokter, apoteker atau perawat Anda. Hal yang sama berlaku untuk efek samping yang tidak tercantum dalam leaflet ini.

Untuk melaporkan efek samping, hubungi www.pfizersafetyreporting.com atau kirimkan email di IDN.AEReporting@pfizer.com

9. Apa saja obat atau makanan lain yang harus dihindari selama menggunakan obat ini?

Sampaikan pada dokter atau apoteker Anda jika Anda meminum, baru-baru ini meminum, atau mungkin meminum obat lain apa pun. IBRANCE dapat mempengaruhi fungsi obat yang lain.

Terutama, yang berikut dapat meningkatkan risiko efek samping dengan IBRANCE:

- Lopinavir, indinavir, nelfinavir, ritonavir, telaprevir, dan saquinavir yang digunakan untuk mengobati infeksi HIV/AIDS.
- Antibiotik klaritromisin dan telitromisin yang digunakan untuk mengobati infeksi bakteri.
- Vorikonazol, itrakonazol, ketokonazol, dan posakonazol yang digunakan untuk mengobati infeksi jamur.
- Nefazodon yang digunakan untuk mengobati depresi.

Obat berikut dapat meningkatkan risiko efek samping saat diberikan dengan IBRANCE:

- Kuinidin yang umumnya digunakan untuk mengobati gangguan irama jantung.
- Kolkisin yang digunakan untuk mengobati radang sendi.
- Pravastatin dan rosuvastatin yang digunakan untuk mengobati kadar kolesterol tinggi.
- Sulfasalazin yang digunakan untuk mengobati artritis reumatoid.
- Alfentanil yang digunakan untuk anestesi dalam pembedahan; fentanil yang digunakan dalam pra-prosedur sebagai pereda nyeri serta sebagai anestesi.
- Siklosporin, everolimus, takrolimus, dan sirolimus yang digunakan dalam transplantasi organ untuk mencegah penolakan.
- Dihidroergotamin dan ergotamin yang digunakan untuk mengobati migrain.
- Pimozid yang digunakan untuk mengobati skizofrenia dan psikosis kronis.
- Midazolam

Obat berikut dapat mengurangi kemanjuran IBRANCE:

- Karbamazepin dan fenitoin, yang digunakan untuk menghentikan kejang.
- Enzalutamid yang digunakan untuk mengobati kanker prostat.
- Rifampin yang digunakan untuk mengobati tuberkulosis (TB).
- St. John’s Wort, produk herbal yang digunakan untuk mengobati depresi ringan dan kecemasan.

IBRANCE dengan makanan dan minuman
Hindari mengonsumsi jeruk bali dan jus jeruk bali saat meminum IBRANCE karena dapat meningkatkan efek samping IBRANCE;

10. Apa yang harus dilakukan jika ada dosis terlewat?
Jika Anda melewatkan dosis atau muntah, minum jadwal berikutnya sesuai jadwal. Jangan meminum dua kali untuk mengganti tablet yang lupa diminum.

11. Bagaimana cara menyimpan obat ini?

- Jauhkan dari jangkauan dan penglihatan anak-anak.
- Jangan meminum obat ini jika kemasannya rusak atau menunjukkan tanda-tanda perusakan.
- Jangan membuang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Tindakan-tindakan ini akan membantu melindungi lingkungan.
- Simpan pada suhu di bawah 30°C.

12. Tanda dan gejala overdosis

Efek samping mana pun yang disebutkan di atas mungkin terjadi.

13. Apa yang harus dilakukan jika Anda menggunakan dosis melebihi anjuran?
Jika Anda meminum IBRANCE melebihi dosis yang disarankan, segera temui dokter atau rumah sakit. Penanganan segera mungkin diperlukan.

Bawa kemasan dan brosur ini, agar dokter tahu obat yang telah diminum.

14. Yang perlu diperhatikan saat menggunakan obat ini
Bicaralah dengan dokter, apoteker, atau perawat sebelum meminum IBRANCE.

IBRANCE dapat mengurangi jumlah sel darah putih dan melemahkan sistem kekebalan tubuh Anda. Oleh karena itu, Anda mungkin berisiko lebih besar terkena infeksi saat meminum IBRANCE.

Sampaikan kepada dokter, apoteker, atau perawat jika Anda mengalami tanda-tanda atau gejala infeksi, seperti menggigil atau demam.

Anda akan menjalani tes darah rutin selama pengobatan untuk memeriksa apakah IBRANCE memengaruhi sel darah Anda (sel darah putih, sel darah merah, dan trombosit).

IBRANCE dapat menimbulkan bekuan darah dalam pembuluh vena. Beri tahu dokter, apoteker, atau perawat Anda jika Anda mengalami tanda-tanda atau gejala bekuan darah dalam pembuluh vena, seperti nyeri atau kaku, pembengkakan, dan kemerahan pada kaki (atau lengan) yang terdampak, nyeri dada, sesak napas, atau pusing.

IBRANCE dapat menyebabkan peradangan paru-paru yang berat atau mengancam jiwa selama pengobatan yang dapat menyebabkan kematian. Segera beri tahu petugas kesehatan Anda jika Anda menunjukkan gejala-gejala baru atau gejala-gejala yang bertambah parah, di antaranya:

- kesulitan bernapas atau sesak napas
- batuk kering
- nyeri dada

15. Kapan sebaiknya Anda berkonsultasi dengan dokter?
Jika Anda memiliki pertanyaan lebih lanjut atau Anda mengalami situasi yang sama seperti yang tercantum dalam brosur ini, konsultasikan dengan dokter, apoteker, atau perawat.

16. Nama produsen/importir/pemegang otorisasi pemasaran
Diproduksi oleh:
Pfizer Manufacturing Deutschland GmbH
Freiburg Im Breisgau
Jerman

Diimpor oleh:
PT. Pfizer Indonesia
Jakarta, Indonesia

Ibrance 75 mg Tablet salut selaput; Dus berisi 1 blister masing-masing berisi 7 tablet salut selaput; No.Reg. DKI2158501617A1
Ibrance 100 mg Tablet salut selaput; Dus berisi 1 blister masing-masing berisi 7 tablet salut selaput; No.Reg. DKI2158501617B1

Ibrance 125 mg Tablet salut selaput; Dus berisi 1 blister masing-masing berisi 7 tablet salut selaput; No.Reg. DKI2158501617C1

17. Tanggal revisi
02/2025

18. Peringatan khusus
HARUS DENGAN RESEP DOKTER