ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 75 mg hard capsules
IBRANCE 100 mg hard capsules
IBRANCE 125 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IBRANCE 75 mg hard capsules
Each hard capsule contains 75 mg of palbociclib.

Excipients with known effect
Each hard capsule contains 56 mg of lactose (as monohydrate).

IBRANCE 100 mg hard capsules
Each hard capsule contains 100 mg of palbociclib.

Excipients with known effect
Each hard capsule contains 74 mg of lactose (as monohydrate).

IBRANCE 125 mg hard capsules
Each hard capsule contains 125 mg of palbociclib.

Excipients with known effect
Each hard capsule contains 93 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

IBRANCE 75 mg hard capsules
Opaque, hard capsule, with a light orange body (printed “PBC 75” in white) and a light orange cap (printed “Pfizer” in white). The capsule length is 18.0 ± 0.3 mm.

IBRANCE 100 mg hard capsules
Opaque, hard capsule, with a light orange body (printed “PBC 100” in white) and a caramel cap (printed “Pfizer” in white). The capsule length is 19.4 ± 0.3 mm.

IBRANCE 125 mg hard capsules
Opaque, hard capsule, with a caramel body (printed “PBC 125” in white) and a caramel cap (printed “Pfizer” in white). The capsule length is 21.7 ± 0.3 mm.

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 an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1).

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.

Posology

The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The treatment with IBRANCE should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

When coadministered 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 Summary of Product Characteristics of letrozole. Treatment of pre/perimenopausal women with the combination of palbociclib plus letrozole should always be combined with an LHRH agonist (see section 4.4).

When coadministered 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 Summary of Product Characteristics of fulvestrant. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

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

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2, and 3 (see sections 4.4 and 4.8).

Table 1. IBRANCE recommended dose modifications for adverse reactions

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

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

Complete blood count should be monitored 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, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle and as clinically indicated.

Absolute neutrophil counts (ANC) of ≥1000/mm^3 and platelet counts of ≥50,000/mm^3 are recommended to receive IBRANCE.

Table 2. IBRANCE dose modification and management – Haematological toxicities

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 subsequent cycles.
Grade 3 ANC[b] (<1000 to 500/mm^3) + Fever ≥38.5 ºC and/or infection	At any time: Withhold IBRANCE until recovery to Grade ≤2 Resume at next lower dose.
Grade 4[a]	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at next lower dose.

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

[a] Table applies to all haematological 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-haematological toxicities

CTCAE Grade	Dose modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-haematological 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.

Special populations

Elderly
No dose adjustment of IBRANCE is necessary in patients ≥65 years of age (see section 5.2).

Hepatic impairment
No dose adjustment of IBRANCE 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 sections 4.4 and 5.2).

Renal impairment
No dose adjustment of IBRANCE is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dose adjustment recommendation in this patient population (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of IBRANCE in children and adolescents ≤18 years of age have not been established. No data are available.

Method of administration

IBRANCE is for oral use. It should be taken with food, preferably a meal to ensure consistent palbociclib exposure (see section 5.2). Palbociclib should not be taken with grapefruit or grapefruit juice (see section 4.5).

IBRANCE capsules should be swallowed whole (should not be chewed, crushed, or opened prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

4.3 Contraindications

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

Use of preparations containing St. John's Wort (see section 4.5).

4.4 Special warnings and precautions for use

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).

Haematological disorders

Dose 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 sections 4.2 and 4.8).

Infections

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

Infections have been reported at a higher rate in patients treated with IBRANCE in randomised clinical studies compared to patients treated in the respective comparator arm. Grade 3 and Grade 4

infections occurred respectively in 4.5% and 0.7% of patients treated with IBRANCE in any combination (see section 4.8).

Patients should be monitored for signs and symptoms of infection and treated as medically appropriate (see section 4.2).

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

Hepatic impairment

Administer IBRANCE with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity (see sections 4.2 and 5.2).

Renal impairment

Administer IBRANCE with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity (see sections 4.2 and 5.2).

Concomitant treatment with inhibitors or inducers of CYP3A4

Strong inhibitors of CYP3A4 may lead to increased toxicity (see section 4.5). 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).

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).

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).

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on the pharmacokinetics of palbociclib

Effect of CYP3A inhibitors
Coadministration of multiple 200 mg doses of itraconazole with a single 125 mg palbociclib dose increased palbociclib total exposure (AUC_{inf}) and the peak concentration (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125 mg palbociclib dose given alone.

The concomitant use of strong CYP3A inhibitors including, but not limited to: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided (see sections 4.2 and 4.4).

No dose adjustments are needed for mild and moderate CYP3A inhibitors.

Effect of CYP3A inducers
Coadministration of multiple 600 mg doses of rifampin with a single 125 mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125 mg palbociclib dose given alone.

The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort should be avoided (see sections 4.3 and 4.4).

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. No dose adjustments are required for moderate CYP3A inducers (see section 4.4).

Effect of acid reducing agents

Under fed conditions (intake of a moderate-fat meal), coadministration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg IBRANCE decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease) compared with a single dose of 125 mg IBRANCE administered alone.

Under fasting conditions, the coadministration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg IBRANCE decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively. Therefore, IBRANCE should be taken with food, preferably a meal (see sections 4.2 and 5.2).

Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, no clinically relevant effect of H2-receptor antagonists or local antacids on palbociclib exposure is expected when palbociclib is taken with food.

Effects of palbociclib on the pharmacokinetics of other medicinal products

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

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

Drug-drug interaction between palbociclib and letrozole

Data from the drug-drug interaction (DDI) evaluation portion of a clinical study in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 medicinal products were coadministered.

Effect of tamoxifen on palbociclib exposure

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

Drug-drug interaction between palbociclib and 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 two medicinal products were coadministered.

Drug-drug interaction between palbociclib and oral contraceptives

DDI studies of palbociclib with oral contraceptives have not been conducted (see section 4.6).

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 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 OCT1 and then may increase the exposure of medical product substrates of this transporter (e.g., metformin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Females of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods (e.g., double-barrier contraception) during therapy and for at least 3 weeks or 14 weeks after completing therapy for females and males, respectively (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). IBRANCE is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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

Fertility

There were no effects on oestrous cycle (female rats) or mating and fertility in rats (male or female) in nonclinical reproductive studies. However, no clinical data have been obtained on fertility in humans. 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). Thus, men may consider sperm preservation prior to beginning therapy with IBRANCE.

4.7 Effects on ability to drive and use machines

IBRANCE has minor influence on the ability to drive and use machines. However, IBRANCE may cause fatigue and patients should exercise caution when driving or using machines.

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, alopecia, and diarrhoea. The most common (≥2%) Grade ≥3 adverse reactions of palbociclib were neutropenia, leukopenia, anaemia, fatigue, and infections.

Dose reductions or dose modifications due to any adverse reaction occurred in 34.4% of patients receiving IBRANCE in randomised clinical studies regardless of the combination.

Permanent discontinuation due to an adverse reaction occurred in 4.1% 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 was 12.7 months.

Table 5 reports the laboratory abnormalities observed in pooled datasets from 3 randomized 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).

Table 4. Adverse reactions based on pooled dataset from 3 randomised studies (N=872)

System Organ Class **Frequency** **Preferred Term**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Infections and infestations			
Very common			
Infections[b]	477 (54.7)	39 (4.5)	6 (0.7)
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	703 (80.6)	482 (55.3)	88 (10.1)
Leukopenia[d]	394 (45.2)	228 (26.1)	5 (0.6)
Anaemia[e]	241 (27.6)	38 (4.4)	2(0.2)
Thrombocytopenia[f]	166 (19.0)	14 (1.6)	3 (0.3)
Common			
Febrile neutropenia	14 (1.6)	10 (1.1)	1 (0.1)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	138 (15.8)	7(0.8)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	74 (8.5)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	38 (4.4)	1 (0.1)	0 (0.0)
Lacrimation increased	50 (5.7)	0 (0.0)	0 (0.0)

Table 4. Adverse reactions based on pooled dataset from 3 randomised studies (N=872)

System Organ Class Frequency Preferred Term	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Dry eye	31 (3.6)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders			
Common			
Epistaxis	73 (8.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Very common			
Stomatitis[g]	252 (28.9)	6 (0.7)	0 (0.0)
Nausea	298 (34.2)	3 (0.3)	0 (0.0)
Diarrhoea	214 (24.5)	9 (1.0)	0 (0.0)
Vomiting	149 (17.1)	4 (0.5)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	144 (16.5)	6 (0.7)	0 (0.0)
Alopecia	226 (25.9)	N/A	N/A
Common			
Dry skin	82 (9.4)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	342 (39.2)	20 (2.3)	2 (0.2)
Asthenia	112 (12.8)	12 (1.4)	0 (0.0)
Pyrexia	108(12.4)	1 (0.1)	0 (0.0)
Investigations			
Common			
ALT increased	70 (8.0)	15 (1.7)	1 (0.1)
AST Increased	75 (8.6)	22 (2.5)	0 (0.0)

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

[a] Preferred Terms (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.

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	97.2	39.6	0.9	25.5	0.2	0.2
Neutrophils decreased	95.5	55.9	10.4	17.2	1.1	0.6
Anaemia	78.6	4.8	N/A	40.5	2.2	N/A
Platelets decreased	62.6	1.6	0.6	12.7	0.2	0.0
AST increased	48.4	3.3	0.0	40.8	1.9	0.0
ALT increased	40.8	2.2	0.1	31.1	0.2	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 703 (80.6%) patients receiving IBRANCE regardless of the combination, with Grade 3 neutropenia being reported in 482 (55.3%) patients, and Grade 4 neutropenia being reported in 88 (10.1 %) 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% patients receiving IBRANCE in combination with fulvestrant and in 2.1% 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 the national reporting system listed in Appendix V.

4.9 Overdose

In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and haematological (e.g., neutropenia) toxicity may occur and general supportive care should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE33.

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 signalling 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 activity against luminal breast cancers, particularly 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). Mechanistic analyses revealed that the combination of palbociclib with antioestrogen agents enhanced the reactivation of Rb through inhibition of Rb phosphorylation resulting in reduced E2F signalling 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 signalling and dose-dependent tumour growth. Studies are ongoing investigating the importance of Rb expression for the activity of palbociclib in fresh tumour 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 efficacy and safety

Randomised Phase 3 Study PALOMA-2: IBRANCE in combination with letrozole

The efficacy of palbociclib in combination with letrozole versus letrozole plus placebo was evaluated in an international, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted in women with ER-positive, HER2-negative locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer who had not received prior systemic treatment for their advanced disease.

A total of 666 postmenopausal women were randomised 2:1 to the palbociclib plus letrozole arm or placebo plus letrozole arm and were stratified by site of disease (visceral versus nonvisceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (*de novo* metastatic versus ≤12 months versus >12 months), and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy versus 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 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 prognostic 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. The majority of patients (97.4%) had metastatic disease at baseline, 23.6% of patients had bone-only disease, and 49.2% of patients had visceral disease.

The primary endpoint of the study was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as assessed by investigator. Secondary efficacy endpoints included objective response (OR), clinical benefit response (CBR), safety, and change in quality of life (QoL).

The study met its primary objective of improving PFS. The observed hazard ratio (HR) was 0.576 (95% confidence interval [CI]: 0.46, 0.72) in favour of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of <0.000001. The median PFS for patients in the palbociclib plus letrozole arm was 24.8 months (95% CI: 22.1, NE) and 14.5 months (95% CI: 12.9, 17.1) for patients in the placebo plus letrozole arm.

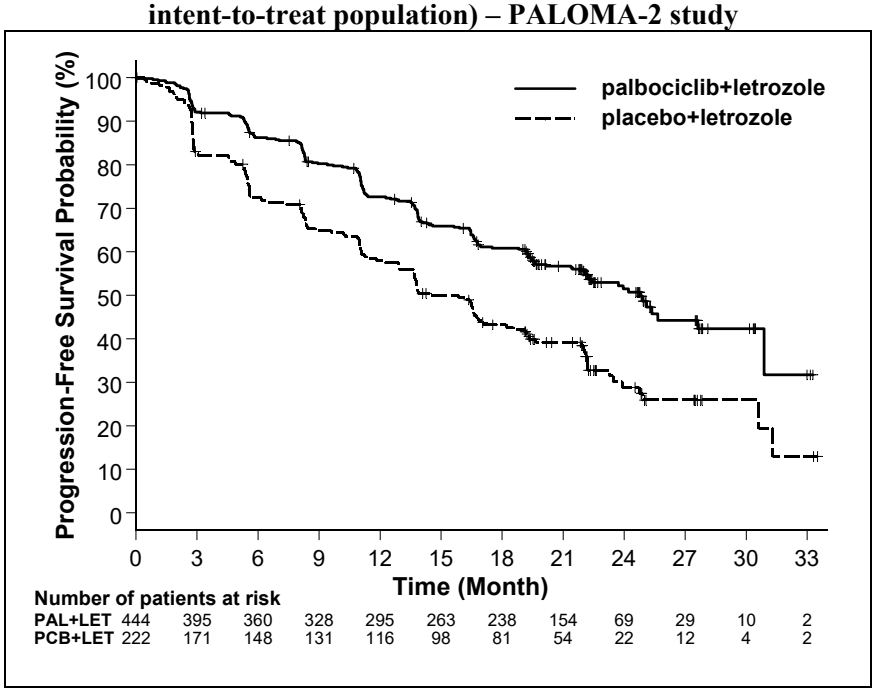
Efficacy data from PALOMA-2 study are summarised in Table 6 and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 6. Efficacy results from PALOMA 2 study (intent-to-treat population)

	26 February 2016 Cutoff	
	IBRANCE plus letrozole (N=444)	**Placebo plus letrozole (N=222)**
Progression-free survival		
Investigator assessment, Number of events (%)	194 (43.7%)	137 (61.7%)
Median [months (95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio (95% CI) and 1-sided p-value	0.576 (0.46, 0.72), p<0.000001	
Independent radiographic review, Number of events (%)	152 (34.2%)	96 (43.2%)
Median [months (95% CI)	30.5 (27.4, NE)	19.3 (16.4, 30.6)
Hazard ratio (95% CI) and 1-sided p-value	0.653 (0.505, 0.84), p=0.000532	
Secondary efficacy endpoints (Investigator assessment)		
OR [% (95% CI)]	46.4 (41.7, 51.2)	38.3 (31.9, 45.0)
OR (measurable disease) [% (95% CI)]	60.7 (55.2, 65.9)	49.1 (41.4, 56.9)
CBR [% (95% CI)]	85.8 (82.2, 88.9)	71.2 (64.7, 77.0)

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

Figure 1. Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population) – PALOMA-2 study



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

A series of prespecified subgroup PFS analyses was performed based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in favor of the palbociclib plus letrozole arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for patients with visceral metastases (HR of 0.67 [95% CI: 0.50, 0.89], median progression-free survival [mPFS] 19.2 months versus 12.9 months) or without visceral metastases (HR of 0.48 [95% CI: 0.34, 0.67], mPFS Not Reached [NR] versus 16.8 months) and patients with bone only disease (HR of 0.36 [95% CI: 0.22, 0.59], mPFS NR vs. 11.2 months) or without bone-only disease (HR of 0.65 [95% CI: 0.51, 0.84], mPFS 22.2 months versus 14.5 months).Similarly, a reduction in the risk of disease progression or death in the palbociclib plus letrozole arm was observed in

512 patients whose tumor tested positive for Rb protein expression by immunohistochemistry (IHC) (HR of 0.531 [95% CI: 0.42, 0.68], mPFS 24.2 months versus 13.7 months). The reduction in risk of disease progression or death in favor of the palbociclib plus letrozole arm was not statistically significant in the 51 patients whose tumors tested negative for Rb protein expression by IHC (HR of 0.675 [95% CI: 0.31, 1.48], mPFS NR versus 18.5 months).

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 7.

Table 7. Efficacy results in visceral and non-visceral disease from PALOMA–2 study (intent-to-treat population)

	Visceral Disease		**Non-visceral Disease**	
	IBRANCE plus letrozole (N=214)	**Placebo plus letrozole (N=110)**	**IBRANCE plus letrozole (N=230)**	**Placebo plus letrozole (N=112)**
OR [% (95% CI)]	58.9 (52.0, 65.5)	45.5 (35.9, 55.2)	34.8 (28.6, 41.3)	31.3 (22.8, 40.7)
TTR, Median [months (range)]	5.4 (2.0, 19.5)	4.1 (2.6, 16.6)	2.9 (2.1, 27.8)	5.5 (2.6, 22.3)

N=number of patients; CI=confidence interval; OR=objective response based on confirmed and unconfirmed responses according to RECIST 1.1; TTR=time to first tumor response.

Randomised Phase 3 Study PALOMA-3: IBRANCE in combination with fulvestrant

The efficacy of palbociclib in combination with fulvestrant versus fulvestrant plus placebo was evaluated in an international, randomised, double-blind, parallel-group, multicentre study conducted in women with HR-positive, HER2-negative locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo)adjuvant or metastatic setting.

A total of 521 pre/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy or on or within 1 month from prior endocrine therapy for advanced disease, were randomised 2:1 to palbociclib 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. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, 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 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 prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. The median age of patients enrolled in this study was 57 years (range 29, 88). In each treatment arm the majority of patients were White, had documented sensitivity to prior hormonal therapy, and were postmenopausal. Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, CBR, OS, safety, and time-to-deterioration (TTD) in pain endpoint.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; 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.

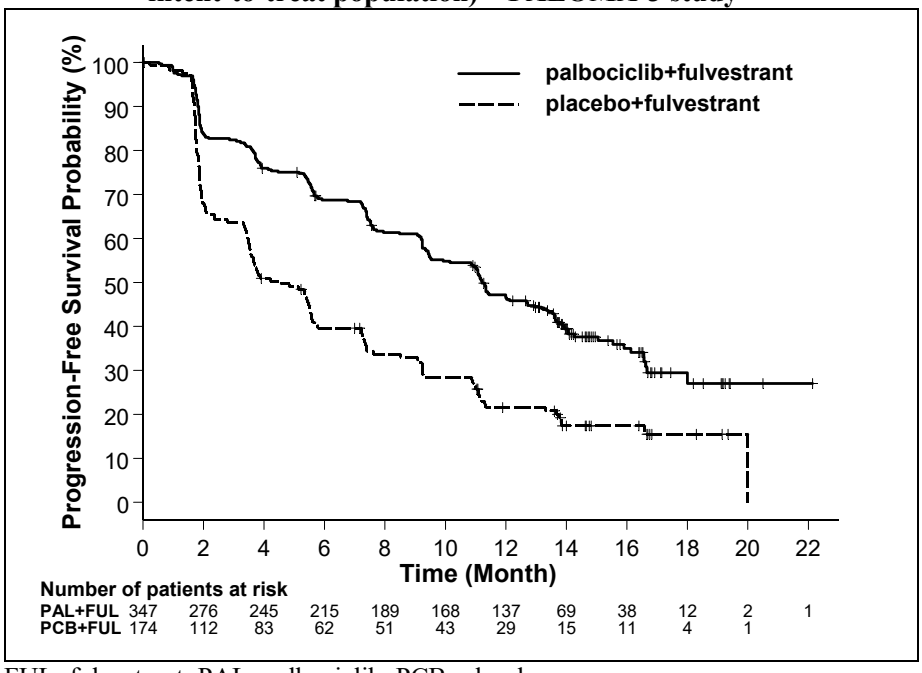
A more mature update of efficacy data is reported in Table 8.

Table 8. Efficacy results – PALOMA-3 study (Investigator assessment, intent-to-treat population)

	Updated analysis (23 October 2015 cutoff)	
	IBRANCE plus fulvestrant (N=347)	**Placebo plus fulvestrant (N=174)**
Progression-free survival (PFS)		
Number of events (%)	200 (57.6)	133 (76.4)
Median [months (95% CI)]	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.497 (0.398, 0.620), p<0.000001	
Secondary efficacy endpoints		
OR [% (95% CI)]	26.2 (21.7, 31.2)	13.8 (9.0, 19.8)
OR (measurable disease) [% (95% CI)]	33.7 (28.1, 39.7)	17.4 (11.5, 24.8)
CBR [% (95% CI)]	68.0 (62.8, 72.9)	39.7 (32.3, 47.3)

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

Figure 2. Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA-3 study



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

A reduction in the risk of disease progression or death in the palbociclib plus fulvestrant arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for pre/perimenopausal women (HR of 0.46 [95% CI: 0.28, 0.75]) and postmenopausal women (HR of 0.52 [95% CI: 0.40, 0.66]) and patients with visceral site of metastatic disease (HR of 0.50 [95% CI: 0.38, 0.65]) and non-visceral site of metastatic disease (HR of 0.48 [95% CI: 0.33, 0.71]). Benefit was also observed regardless of lines of prior therapy in the

metastatic setting, whether 0 (HR of 0.59 [95% CI: 0.37, 0.93]), 1 (HR of 0.46 [95% CI: 0.32, 0.64]), 2 (HR of 0.48 [95% CI: 0.30, 0.76]), or ≥3 lines (HR of 0.59 [95% CI: 0.28, 1.22]). Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 9.

Table 9. Efficacy results in visceral and non-visceral disease from PALOMA–3 study (Intent-to-Treat population)

	Visceral Disease		Non-visceral Disease	
	IBRANCE plus fulvestrant (N=206)	**Placebo plus fulvestrant (N=105)**	**IBRANCE plus fulvestrant (N=141)**	**Placebo plus fulvestrant (N=69)**
OR [%, (95% CI)]	35.0 (28.5, 41.9)	13.3 (7.5, 21.4)	13.5 (8.3, 20.2)	14.5 (7.2, 25.0)
TTR, Median [months (range)]	3.8 (3.5, 16.7)	5.4 (3.5, 16.7)	3.7 (1.9, 13.7)	3.6 (3.4, 3.7)

N=number of patients; CI=confidence interval; OR= objective response based on confirmed and unconfirmed responses according to RECIST 1.1; TTR=time to first tumor response.

Patient-reported symptoms were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the fulvestrant only arm completed the questionnaire at baseline and at least 1 postbaseline visit.

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

The European Medicines Agency has waived the obligation to submit the results of studies with IBRANCE in all subsets of the paediatric population in the treatment of breast carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of palbociclib were characterised in patients with solid tumours including advanced breast cancer and in healthy volunteers.

Absorption

The mean C_{max} of palbociclib is generally observed between 6 to 12 hours following oral administration. 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 area under the curve (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

Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Compared to palbociclib given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake significantly reduced the intersubject and intrasubject

variability of palbociclib exposure. Based on these results, palbociclib should be taken with food (see section 4.2).

Distribution

Binding of palbociclib to human plasma proteins *in vitro* was ~85%, with no concentration dependence. 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. *In vitro*, the uptake of palbociclib into human hepatocytes occurred mainly via passive diffusion. Palbociclib is not a substrate of OATP1B1 or OATP1B3.

Biotransformation

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 sulphonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma.

The majority of the material was excreted as metabolites. In faeces, 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 sulphotransferase (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 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 92% of the total administered radioactive dose was recovered in 15 days; faeces (74% of dose) was the major route of excretion, with 17% of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2% and 7% of the administered dose, respectively.

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.

In vitro evaluations indicate that palbociclib has low potential to inhibit the activities of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, and bile salt export pump (BSEP) at clinically relevant concentrations.

Special populations

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 38 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.

Paediatric population
Pharmacokinetics of palbociclib has not been evaluated in patients ≤18 years of age.

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 (Child-Pugh class C) hepatic impairment, 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 of palbociclib.

Renal impairment
Data from a pharmacokinetic trial in subjects with varying degrees of renal function indicate that 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 (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 pharmacokinetics of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring haemodialysis.

Ethnicity
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.

5.3 Preclinical safety data

The primary target organ findings of potential relevance to humans included haematolymphopoietic and male reproductive organ effects in rats and dogs in studies up to 39 weeks duration. Effects on glucose metabolism were associated with findings in the pancreas and secondary effects on eye, teeth, kidney, and adipose tissue in studies ≥15 weeks duration in rats only and bone changes were observed in rats only following 27 weeks of dosing. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. 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}. The reversibility of the effects on glucose homeostasis, pancreas, eye, kidney, and bone was not established following a 12-week nondosing period, whereas partial to full reversal of effects on the haematolymphopoietic and male reproductive systems, teeth, and adipose tissue was observed.

Carcinogenicity

Carcinogenicity studies have not been conducted with palbociclib.

Genotoxicity

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

Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells *in vitro* and in the bone marrow of male rats at doses ≥100 mg/kg/day. The exposure of animals at 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 ≥7 times or subtherapeutic compared to human clinical exposure based on AUC, respectively. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week nondosing 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 is a reversible inhibitor of cyclin-dependent kinases 4 and 6, which are both involved in regulating the cell cycle. It may therefore have risk of foetal harm if used during pregnancy. Palbociclib was foetotoxic 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 foetal 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 foetal exposure and cross-placenta transfer have not been examined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate type A
Colloidal anhydrous silica
Magnesium stearate

Capsule shell

Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)

Printing ink

Shellac
Titanium dioxide (E171)
Ammonium hydroxide (28% solution)
Propylene glycol
Simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE/PVC/Al blister strip containing 7 hard capsules (one capsule per cell). Each carton contains 21 hard capsules (3 blister strips per pack).

HDPE bottle with a PP closure containing 21 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

IBRANCE 75 mg hard capsules
EU/1/16/1147/001
EU/1/16/1147/002

IBRANCE 100 mg hard capsules
EU/1/16/1147/003
EU/1/16/1147/004

IBRANCE 125 mg hard capsules
EU/1/16/1147/005
EU/1/16/1147/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 November 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 75 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 75 mg hard capsules
palbociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 75 mg palbociclib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1147/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IBRANCE 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

75 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 75 mg hard capsules
palbociclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 75 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 75 mg hard capsules
palbociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 75 mg palbociclib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1147/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IBRANCE 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 100 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 100 mg hard capsules
palbociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 100 mg palbociclib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1147/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IBRANCE 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

100 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 100 mg hard capsules
palbociclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 100 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 100 mg hard capsules
palbociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 100 mg palbociclib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1147/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IBRANCE 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 125 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 125 mg hard capsules
palbociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 125 mg palbociclib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1147/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IBRANCE 125 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

125 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 125 mg hard capsules
palbociclib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 125 MG CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

IBRANCE 125 mg hard capsules
palbociclib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 125 mg palbociclib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1147/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

IBRANCE 125 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IBRANCE 75 mg hard capsules
IBRANCE 100 mg hard capsules
IBRANCE 125 mg hard capsules
palbociclib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IBRANCE is and what it is used for
2. What you need to know before you take IBRANCE
3. How to take IBRANCE
4. Possible side effects
5. How to store IBRANCE
6. Contents of the pack and other information

1. What IBRANCE is and what it is used for

IBRANCE is an anticancer medicine containing the active substance palbociclib.

Palbociclib works by blocking proteins called cyclin-dependent kinase 4 and 6, which regulate cell growth and division. Blocking these proteins can slow down growth of cancer cells and delay the progression of your cancer.

IBRANCE is used to treat patients with certain types of breast cancer (hormone receptor-positive, human epidermal growth factor receptor 2-negative) which have spread beyond the original tumour and/or to other organs. It is given together with aromatase inhibitors or fulvestrant, which are used as hormonal anticancer therapies.

2. What you need to know before you take IBRANCE

Do not take IBRANCE:

- if you are allergic to palbociclib or any of the other ingredients of this medicine (listed in section 6).
- use of preparations containing St. John’s Wort should be avoided while you are taking IBRANCE.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking IBRANCE.

IBRANCE may reduce the number of your white blood cells and weaken your immune system. Therefore, you may be at greater risk of getting an infection while you are taking IBRANCE.

Tell your doctor, pharmacist or nurse if you experience signs or symptoms of an infection, such as chills or fever.

You will have regular blood tests during treatment to check whether IBRANCE affects your blood cells (white blood cells, red blood cells, and platelets).

Children and adolescents

IBRANCE is not to be used in children or adolescents (aged 18 years or under).

Other medicines and IBRANCE

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. IBRANCE may affect the way some other medicines work.

In particular, the following may increase the risk of side effects with IBRANCE:
- Lopinavir, indinavir, nelfinavir, ritonavir, telaprevir, and saquinavir used to treat HIV infection/AIDS.
- Clarithromycin and telithromycin antibiotics used to treat bacterial infections.
- Voriconazole, itraconazole, ketoconazole, and posaconazole used to treat fungal infections.
- Nefazodone used to treat depression.

The following medicines may have increased risk of side effects when given with IBRANCE:
- Quinidine generally used to treat heart rhythm problems.
- Colchicine used to treat gout.
- Pravastatin and rosuvastatin used to treat high cholesterol levels.
- Sulfasalazine used to treat rheumatoid arthritis.
- Alfetanil used for anaesthesia in surgery; fentanyl used in pre-procedures as a pain reliever as well as an anaesthetic.
- Ciclosporin, everolimus, tacrolimus, and sirolimus used in organ transplantation to prevent rejection.
- Dihydroergotamine and ergotamine used to treat migraine.
- Pimozide used to treat schizophrenia and chronic psychosis.

The following medicines may reduce the effectiveness of IBRANCE:
- Carbamazepine and phenytoin, used to stop seizures or fits.
- Enzalutamide to treat prostate cancer.
- Rifampin used to treat tuberculosis (TB).
- St. John’s Wort, a herbal product used to treat mild depression and anxiety.

IBRANCE with food and drink

Avoid grapefruit and grapefruit juice while you are taking IBRANCE as it may increase the side effects of IBRANCE.

Pregnancy and breast-feeding and fertility

You should not use IBRANCE if you are pregnant.

You should avoid becoming pregnant while taking IBRANCE.

Discuss contraception with your doctor if there is any possibility that you or your partner may become pregnant.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Women of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods (e.g., double-barrier contraception such as condom and diaphragm). These methods should be used during therapy and for at least 3 weeks after completing therapy for females and for at least 14 weeks for males.

Breast-feeding
You should not breast-feed while taking IBRANCE. It is not known if IBRANCE is excreted in breast milk.

Fertility
Palbociclib may decrease fertility in men.

Therefore, men may consider sperm preservation before taking IBRANCE.

Driving and using machines

Tiredness is a very common side effect. If you feel unusually tired, take special care when driving or using machines**.**

IBRANCE contains lactose
This medicine contains lactose (found in milk or dairy products). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take IBRANCE

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 125 mg of IBRANCE taken once a day for 3 weeks followed by 1 week without taking IBRANCE. Your doctor will tell you how many capsules of IBRANCE to take.

If you experience certain side effects while you are taking IBRANCE (see section 4 “Possible side effects”), your doctor may lower your dose or stop treatment, either temporarily or permanently. The dose may be lowered to one of the other available strengths 100 mg or 75 mg.

Take IBRANCE once a day at about the same time every day with food, preferably a meal.

Swallow the capsule whole with a glass of water. Do not chew or crush the capsules. Do not open the capsules.

If you take more IBRANCE than you should

If you have taken too much IBRANCE, see a doctor or go to a hospital immediately. Urgent treatment may be necessary.

Take the carton and this leaflet, so that the doctor knows what you have been taking.

If you forget to take IBRANCE

If you miss a dose or vomit, take your next dose as scheduled. Do not take a double dose to make up for the forgotten capsules.

If you stop taking IBRANCE

Do not stop taking IBRANCE unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them:

Contact your doctor immediately if you have any of these symptoms: fever, chills, weakness, shortness of breath, bleeding, or easy bruising which could be a sign of a serious blood disorder.

Other side effects with IBRANCE may include:

Very common side effects (may affect more than 1 in 10 people):
- Infections
- Reduction in white blood cells, red blood cells, and blood platelets
- Feeling of tiredness
- Decreased appetite
- Inflammation of the mouth and lips (stomatitis), nausea, vomiting, diarrhoea
- Rash
- Hair loss
- Weakness
- Fever

Common side effects (may affect up to 1 in 10 people):
- Fever with a drop in the white blood cell count (febrile neutropenia)
- Blurred vision, increased tearing, dry eye
- Abnormalities in liver blood tests
- Alteration in taste (dysgeusia)
- Nosebleed
- Dry skin

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IBRANCE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle or blister and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IBRANCE contains
- The active substance is palbociclib. IBRANCE hard capsules come in different strengths.
- IBRANCE 75 mg hard capsule: each capsule contains 75 mg palbociclib.
- IBRANCE 100 mg hard capsule: each capsule contains 100 mg palbociclib.
- IBRANCE 125 mg hard capsule: each capsule contains 125 mg palbociclib.
- The other ingredients are:
  Capsule content: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate type A, colloidal anhydrous silica, magnesium stearate. Capsule shell: gelatin, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171). Printing ink: shellac, titanium dioxide (E171), ammonium hydroxide (28% solution), propylene glycol, simeticone (see section 2 “IBRANCE contains lactose”).

What IBRANCE looks like and contents of the pack
- IBRANCE 75 mg is supplied as opaque, hard capsules, with a light orange body (printed “PBC 75” in white) and a light orange cap (printed “Pfizer” in white).
- IBRANCE 100 mg is supplied as opaque, hard capsules, with a light orange body (printed “PBC 100” in white) and a caramel cap (printed “Pfizer” in white).
- IBRANCE 125 mg is supplied as opaque, hard capsules, with a caramel body (printed “PBC 125” in white) and a caramel cap (printed “Pfizer” in white).

It is available in blister packs of 21 hard capsules and in plastic bottles of 21 hard capsules.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.