NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IBRANCE® palbociclib 75 mg capsules
IBRANCE® palbociclib 100 mg capsules
IBRANCE® palbociclib 125 mg capsules
IBRANCE® palbociclib 75 mg tablets
IBRANCE® palbociclib 100 mg tablets
IBRANCE® palbociclib 125 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IBRANCE capsule contains palbociclib 75 mg, 100 mg or 125 mg.

Each IBRANCE tablet contains palbociclib 75 mg, 100 mg or 125 mg.

Excipient(s) with known effect

IBRANCE capsules contain lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

IBRANCE is supplied as hard capsules or film-coated tablets for oral administration.

75 mg strength: Opaque, hard capsule, with a light orange body (printed “PBC 75” in white) and a light orange cap (printed “Pfizer” in white). Round, light purple, film-coated tablet debossed with “Pfizer” on one side and “PBC 75” on the other side.

100 mg strength: Opaque, hard capsule, with a light orange body (printed “PBC 100” in white) and a caramel cap (printed “Pfizer” in white). Oval, green, film-coated tablet debossed with “Pfizer” on one side and “PBC 100” on the other side.

125 mg strength: Opaque, hard capsule, with a caramel body (printed “PBC 125” in white) and a caramel cap (printed “Pfizer” in white). Oval, light purple, film-coated tablet debossed with “Pfizer” on one side and “PBC 125” on the other side.

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.

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

4.2. Dose and method of administration

The recommended dose is 125 mg of palbociclib capsule or tablet 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 aromatase inhibitor should be administered according to the dose schedule reported in the Data Sheet. Treatment of pre/perimenopausal women with the combination of palbociclib plus endocrine therapy 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. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with an LHRH agonist 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 modifications

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.

Absolute neutrophil counts (ANC) of $\geq 1000/mm^3$ and platelet counts of $\geq 50{,}000/mm^3$ are recommended to receive IBRANCE.

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 beginning of a cycle and as clinically indicated.

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 ≥38.5ºC 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.

Permanently discontinue IBRANCE in patients with severe interstitial lung disease (ILD) or pneumonitis (see section 4.4).

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 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 section 5.2).

Elderly

No dose adjustment of IBRANCE is necessary in patients ≥65 years of age (see section 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. IBRANCE capsules 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 tablets may be taken with or without food.

IBRANCE capsules or tablets should be swallowed whole (do not chew, crush, open the capsules or split the tablets prior to swallowing). No capsule or tablet should be ingested if it is broken, cracked, or otherwise not intact.

4.3. Contraindications

Hypersensitivity to palbociclib or to any of the excipients.

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.

Neutropenia

Decreased neutrophil counts have been observed in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) or fulvestrant (PALOMA-3), Grade 3 and Grade 4 decreased neutrophil counts were reported in 56.1% and 10.6% of patients, respectively.

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.

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.

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).

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 (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4 and no fatal cases were reported (see section 4.8). Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, 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).

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.

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).

Lactose

IBRANCE 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 medicines 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 rifampicin 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, rifampicin, 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

IBRANCE capsules

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 capsules decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease) compared with a single 125 mg IBRANCE capsule administered alone.

Under fasting conditions, the coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE capsule decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively when compared with a single 125 mg IBRANCE capsule administered alone. Therefore, IBRANCE capsules 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.

IBRANCE film-coated tablets

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 Dose and method of administration).

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, ciclosporine, 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, pravastatin) or BCRP (e.g., 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

Effects on fertility

No clinical data have been obtained on fertility in humans. There were no effects on the oestrous cycle (female rats) or mating and fertility in rats (male or female) in nonclinical reproductive studies.

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. Based on male reproductive organ findings in nonclinical safety studies, male fertility may be compromised by treatment with palbociclib. Thus, men may consider sperm preservation prior to beginning therapy with IBRANCE.

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.

Use in pregnancy - Australian Pregnancy Category D

IBRANCE is not recommended during pregnancy. There are no or limited amount of data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity.

Palbociclib is a reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6, which are both involved in regulating the cell cycle. It may therefore have risk of fetal harm if used during pregnancy. 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.

Women of childbearing potential

Women of childbearing potential who are receiving IBRANCE, 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.

Use in lactation

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.

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

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, fatigue, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and thrombocytopenia.

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.

The most frequently (≥1%) reported serious adverse drug reactions in patients receiving palbociclib plus letrozole (PALOMA-1 and PALOMA-2) were infections (4.6%) and febrile neutropenia (1.3%).

The most frequently (≥1%) reported serious adverse drug reactions in patients receiving palbociclib plus fulvestrant (PALOMA-3) were infections (4.1%), pyrexia (1.4%) and neutropenia (1.2%).

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.

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[a]	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations			
Very common			
Infections[b]	525 (60.2)	55 (6.3)	12 (1.4)
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	719 (82.5)	495 (56.8)	105 (12.0)
Leukopenia[d]	436 (50.0)	264 (30.3)	7 (0.8)
Anaemia[e]	269 (30.8)	50 (5.7)	2 (0.2)
Thrombocytopenia[f]	202 (23.2)	18 (2.1)	4 (0.5)
Common			
Febrile neutropenia	14 (1.6)	12 (1.4)	2 (0.2)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	165 (18.9)	9 (1.0)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	58 (6.7)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Lacrimation increased	63 (7.2)	1 (0.1)	0 (0.0)
Vision blurred	49 (5.6)	1 (0.1)	0 (0.0)
Dry eye	41 (4.7)	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]	14 (1.6)	1 (0.1)	0 (0.0)
Gastrointestinal disorders			
Very common			
Nausea	319 (36.6)	5 (0.6)	0 (0.0)
Stomatitis[g]	278 (31.9)	8 (0.9)	0 (0.0)
Diarrhoea	248 (28.4)	10 (1.1)	0 (0.0)
Vomiting	171 (19.6)	6 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Alopecia	236 (27.1)	0 (0.0)	0 (0.0)
Rash[h]	169 (19.4)	9 (1.0)	0 (0.0)
Dry skin	101 (11.6)	0 (0.0)	0 (0.0)
Common			
Palmar-plantar erythrodysaesthesia syndrome[*]	16 (1.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	366 (42.0)	28 (3.2)	2 (0.2)
Asthenia	123 (14.1)	14 (1.6)	1 (0.1)
Pyrexia	122 (14.0)	1 (0.1)	0 (0.0)
Investigations			
Very Common			
ALT increased	112 (12.8)	25 (2.9)	0 (0.0)
AST Increased	103 (11.8)	19 (2.2)	2 (0.2)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = interstitial lung disease; N/n = number

of patients; N/A = not applicable.
[*] Adverse Drug Reaction (ADR) identified post-marketing.
[a] Preferred Terms (PTs) are listed according to MedDRA 25.1.
[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 ulcer, 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).

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) 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

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.

For information on the management of an overdose, contact the National Poisons Centre on 0800 764 766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

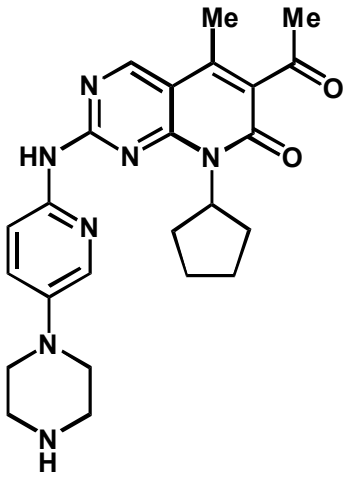
Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE33.

Mechanism of action

Palbociclib is a highly selective, reversible inhibitor of CDK 4 and 6. Cyclin D1 and CDK4/6

are downstream of multiple signalling pathways which lead to cellular proliferation.

Chemical structure of palbociclib



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 trials section. 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) change from baseline and pharmacokinetic data in 77 patients with breast cancer. The upper bound of the one sided 95% CI for the increase from baseline in QTc at all time points at steady state concentrations at the recommended dose of 125 mg (Schedule 3/1) was less than 8 msec. Therefore, at the recommended dose, no palbociclib relevant effects on QT have been observed.

Clinical trials

<u>Randomised Phase 3 Study PALOMA-2: IBRANCE in combination with letrozole</u>

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 estrogen receptor (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).

At the data cutoff date of 26-February-2016, 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.

An updated analysis of the primary and secondary endpoints was performed after an 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.

Table 5 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.

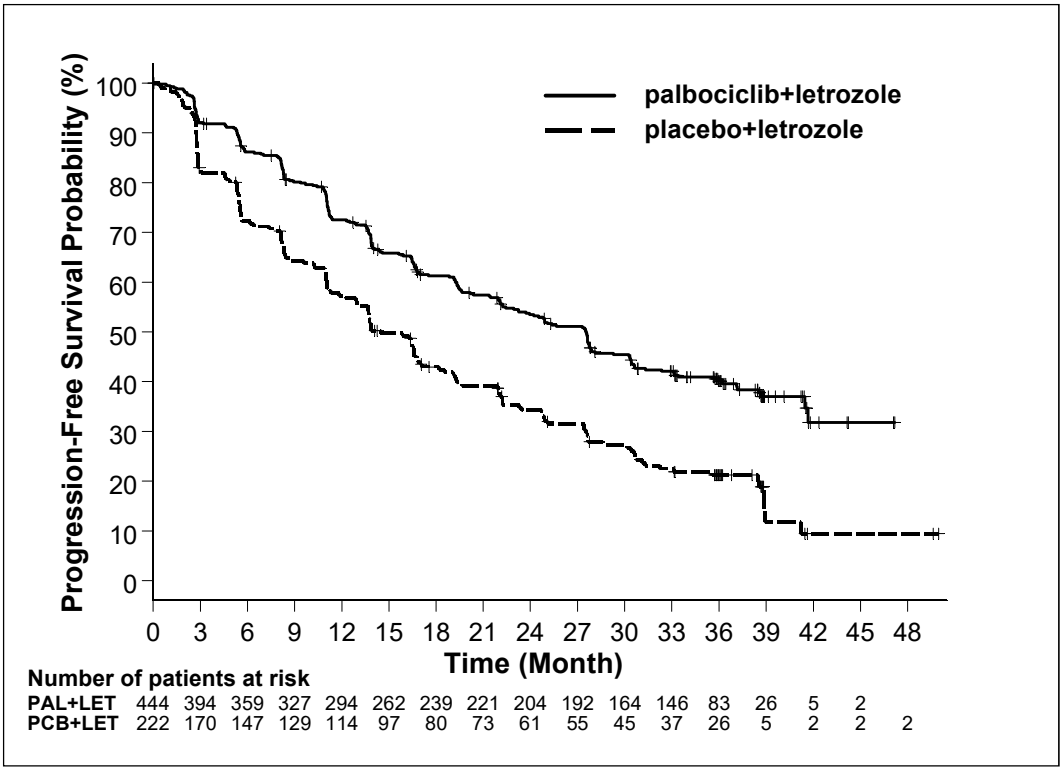
Table 5. PALOMA-2 study (intent-to-treat population): Efficacy results based on primary and updated cutoff dates

	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)]	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	
ORR* [% (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)
ORR* 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)
CBRR* [% (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; ORR=objective response rate; CBRR=clinical benefit response rate; 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 cutoff date)*



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 in the primary and in the updated analysis.

Based on the 31-May-2017 data cutoff date, this reduction in risk continued to be observed in the following subgroups: (1) patients with either visceral metastases (HR of 0.62 [95% CI: 0.47, 0.81], median progression-free survival [mPFS] 19.3 months versus 12.3 months) or without visceral metastases (HR of 0.50 [95% CI: 0.37, 0.67], mPFS 35.9 months versus 17.0 months) and (2) patients with either bone only disease (HR of 0.41 [95% CI: 0.26, 0.63], mPFS 36.2 months versus 11.2 months) or without bone-only disease (HR of 0.62 [95% CI: 0.50, 0.78], mPFS 24.2 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 tumour tested positive for Rb protein expression by immunohistochemistry (IHC) (HR of 0.543 [95% CI: 0.433, 0.681], mPFS 27.4 months versus 13.7 months)]. The reduction in risk of disease progression or death was also reported in the 51 patients whose tumours tested negative for Rb protein expression by IHC (HR of 0.868 [95% CI: 0.424, 1.777], mPFS 23.2 versus 18.5 months.

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease based on the 31-May-2017 updated cutoff date are displayed in Table 6.

Table 6. PALOMA–2 study (intent-to-treat population): Efficacy results in patients with visceral or non-visceral disease *(31-May-2017 cutoff date)*

	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)]	59.8 (52.9, 66.4)	46.4 (36.8, 56.1)	36.1 (29.9, 42.7)	31.3 (22.8, 40.7)
TTR, Median [months (range)]	5.4 (2.0, 30.4)	5.3 (2.6, 27.9)	3.0 (2.1, 27.8)	5.5 (2.6, 22.2)

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

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

The results of the times to initiation of the first and the second subsequent systemic anticancer therapy analyses suggest that the improvement in PFS observed with the addition of palbociclib to letrozole in the first-line treatment setting delayed the initiation of first and second subsequent anticancer therapy. Similarly, first-line palbociclib plus letrozole therapy delayed the initiation of first subsequent chemotherapy compared with placebo plus letrozole.

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

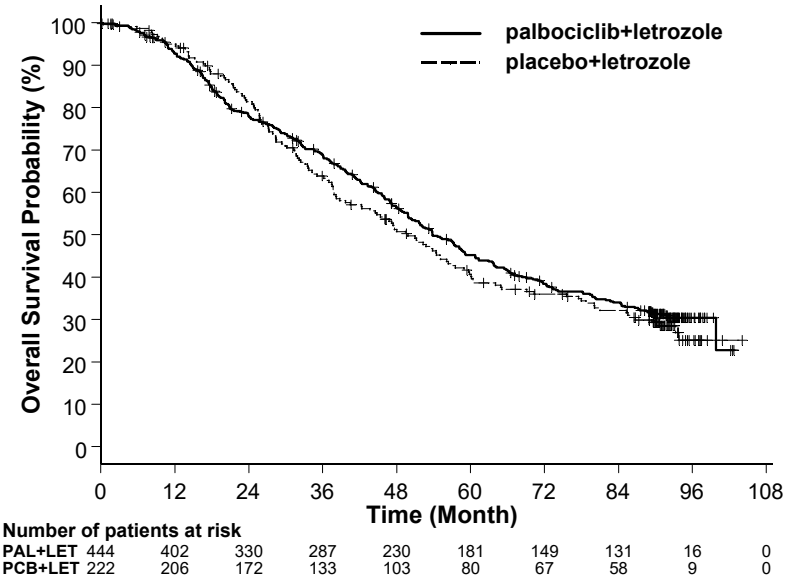
Final Overall Survival (OS) (15 November 2021 Cutoff)		
	Palbociclib plus letrozole (N = 444)	**Placebo plus letrozole (N = 222)**
Number of OS events (%)	287 (64.6)	148 (66.7)
Number of subjects remaining in follow-up (%)	116 (26.1)	48 (21.6)
Median OS (months, 95% CI)	53.8 (49.8, 59.2)	49.8 (42.3, 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 randomisation.

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



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, Overall Survival (OS), safety, and time-to-deterioration (TTD) in pain endpoint. Consistent results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy and menopausal status. The OS data were not mature at the time of the final PFS analysis (11% of patients had died).

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.

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (59.5% of randomised 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.

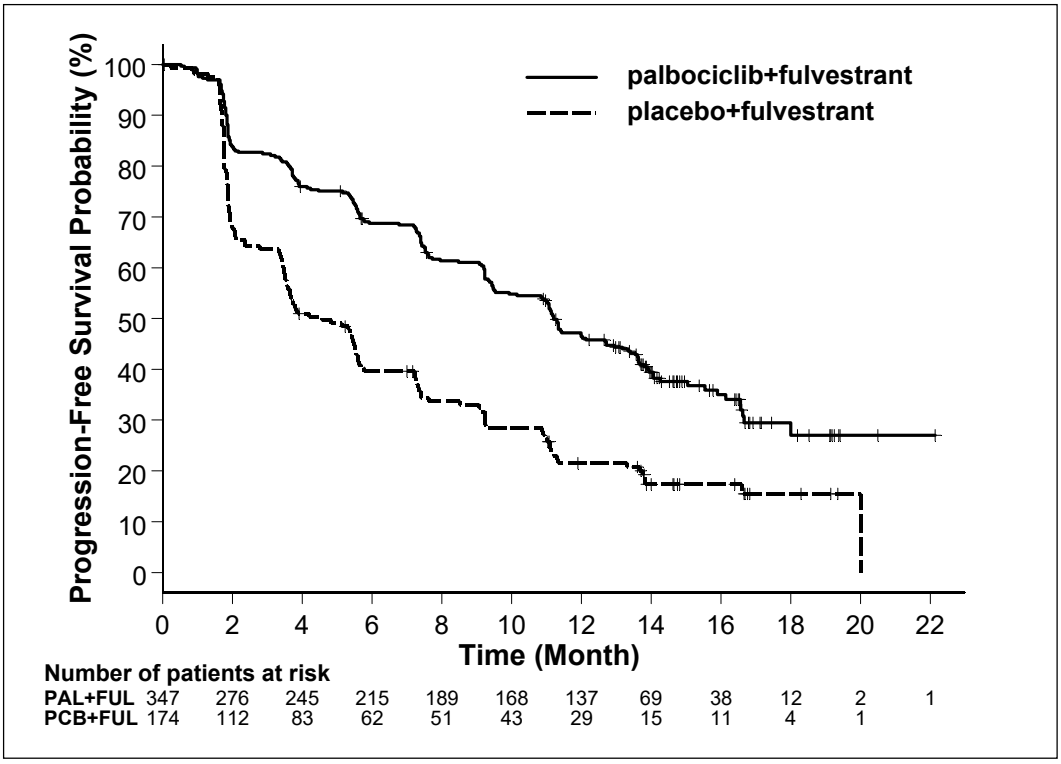
A higher proportion of patients in the placebo plus fulvestrant arm received post-progression systemic treatments overall in comparison with the patients in the palbociclib plus fulvestrant arm (80.5% versus 71.8%) respectively. Also, in placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post progression subsequent treatments.The results from the investigator-assessed PFS and final OS data from PALOMA-3 Study are presented in Table 9. The relevant Kaplan-Meier plots are shown in Figures 3 and 4, respectively.

Table 9. PALOMA-3 study: Efficacy Results (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)]	21.0 (16.9, 25.7)	8.6 (4.9, 13.8)
OR (measurable disease) [% (95% CI)]	27.3 (22.1, 33.1)	10.9 (6.2, 17.3)
DOR (measurable disease) [months (95% CI)]	10.4 (8.3, NE)	9.0 (5.6, NE)
CBR [% (95% CI)]	66.3 (61.0, 71.2)	39.7 (32.3, 47.3)
Final OS analysis *(13 April 2018 cutoff)*		
	IBRANCE plus fulvestrant N=347	**Placebo plus fulvestrant N=174**
Overall Survival		
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†§	

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;
*Response endpoints based on confirmed responses.
† 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.
§ Not statistically significant

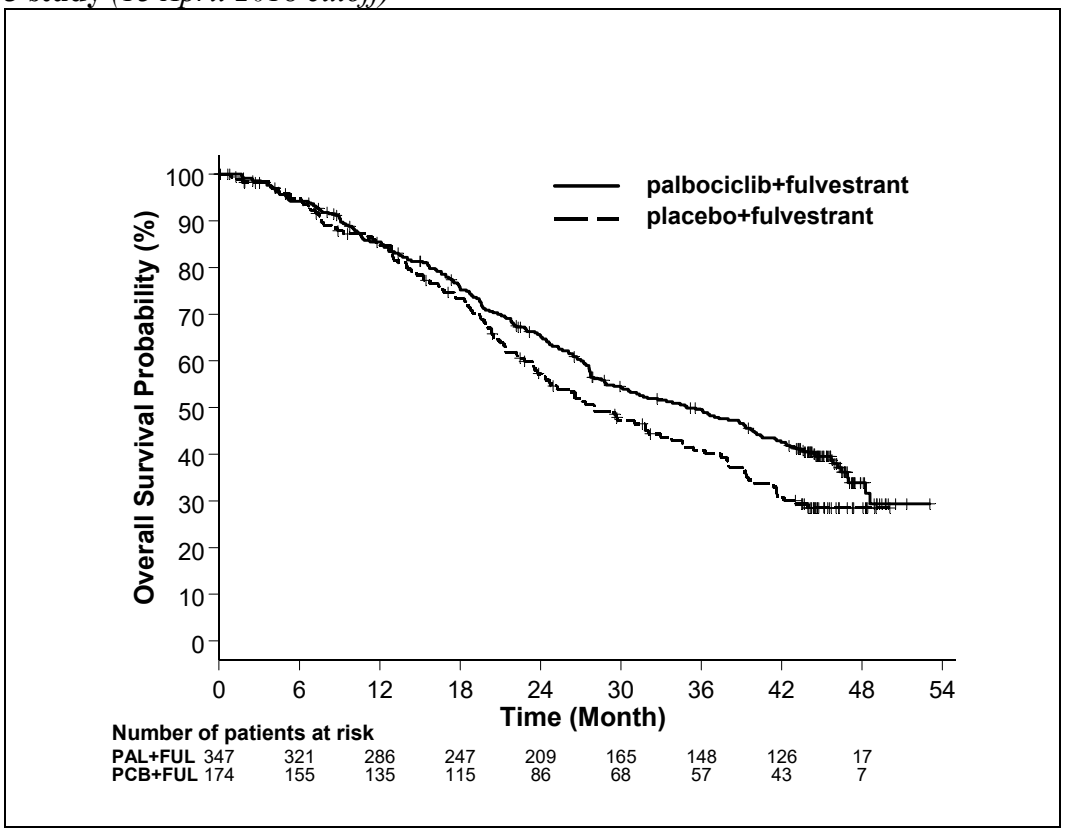
Figure 3. Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA-3 study *(23 October 2015 cutoff)*



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]).

Figure 4. Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA-3 study *(13 April 2018 cutoff)*



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

A positive 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 randomisation are reported in Table 10 below.

Table 10. PALOMA 3 study: 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 Ratios; 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.

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 11.

Table 11. PALOMA 3 study: Efficacy results in visceral and non-visceral disease (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)]	28.0 (21.7, 34.3)	6.7 (2.7, 13.3)	11.3 (6.6, 17.8)	11.6 (5.1, 21.6)
TTR*, Median [months (range)]	3.8 (3.5, 14.0)	3.6 (3.5, 7.4)	3.7 (1.9, 5.7)	3.6 (3.4, 3.7)

*Response results based on confirmed responses.
N=number of patients; CI=confidence interval; OR= objective response; TTR=time to first tumour 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).

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 of IBRANCE capsules. 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 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

IBRANCE capsules

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, IBRANCE capsules should be taken with food (see section 4.2).

IBRANCE film-coated tablets

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

IBRANCE capsules

In a healthy subject study, coadministration of a single 125 mg IBRANCE capsule with multiple doses of the PPI rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease), when compared to a single 125 mg IBRANCE capsule administered alone. Given the reduced effect on gastric pH of H2 receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists or local antacids on palbociclib exposure. In another healthy subject study, coadministration of a single 125 mg IBRANCE capsule with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with a single 125 mg IBRANCE capsule administered alone.

IBRANCE film-coated tablets

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. 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 [14C]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 (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}) 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 has not been studied in patients requiring haemodialysis.

Ethnicity

While palbociclib geometric mean AUC_{inf} and C_{max} values were 30% and 35% higher in Japanese healthy subjects compared with those in non-Asian healthy subjects, palbociclib geometric mean steady-state C_{trough} values were similar in Japanese, Asian (excluding Japanese), and non-Asian advanced breast cancer patients in PALOMA-3. In addition, the safety profile of palbociclib in Japanese patients was similar to that in non Japanese patients following administration of palbociclib 125 mg once daily according to Schedule 3/1. No dose adjustment based on Japanese ethnicity is 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

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 tumours 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 exposure of animals at the no observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

IBRANCE capsules

Capsule content

Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate type A
Silicon dioxide Magnesium stearate

Capsule shell

Gelatin
Iron oxide red (E172)
Iron oxide yellow (E172)
Titanium dioxide (E171)

Printing ink

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

The capsules are opaque and are differentiated by size, colour and printing. The capsule shells consist of a light orange body/light orange cap (75 mg), a light orange body/caramel cap (100 mg) and a caramel body/caramel cap (125 mg).

IBRANCE film-coated tablets

Tablet core:

Microcrystalline cellulose
Silicon dioxide
Crospovidone
Magnesium stearate
Succinic acid

Film coating:

Hypromellose
Titanium dioxide
Triacetin
Indigo carmine aluminium lake
Iron oxide red (75 mg and 125 mg tablets only)
Iron oxide yellow (100 mg tablets only).

The tablets are differentiated by shape, colour and debossing. The 75 mg tablet is round shaped and light purple, the 100 mg tablet is oval shaped and green, the 125 mg tablet is oval shaped and light purple.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 30°C.

IBRANCE tablets: store in the original blister package to protect from moisture.

6.5. Nature and contents of container

IBRANCE 75 mg, 100 mg, and 125 mg capsules are supplied in HDPE bottles or PVC/PCFTE/PVC Al blister packs containing 21 capsules.

IBRANCE 75 mg, 100 mg and 125 mg film-coated tablets are supplied in PVC/OPA/Al/PVC Al blister packs containing 21 tablets.

Not all pack sizes may be available.

6.6. Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140.
Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

29 June 2017

10. DATE OF REVISION OF THE TEXT

4 May 2023

Summary Table of Changes

Section changed	Summary of new information
4.8	Addition of Palmar-plantar erythrodysaesthesia syndrome as postmarketing ADR and update of ADR frequencies
8	Addition of new sponsor website