PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PALBOCICLIB 75 mg TABLETS PFIZER

PALBOCICLIB 100 mg TABLETS PFIZER

PALBOCICLIB 125 mg TABLETS PFIZER

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PALBOCICLIB 75 mg TABLETS PFIZER: each film-coated tablet contains 75 mg palbociclib.

PALBOCICLIB 100 mg TABLETS PFIZER: each film-coated tablet contains 100 mg palbociclib.

PALBOCICLIB 125 mg TABLETS PFIZER: each film-coated tablet contains 125 mg palbociclib.

Sugar-free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

PALBOCICLIB 75 mg TABLETS PFIZER

Round light purple film-coated tablet with " Pfizer"' debossed on one tablet face and " PBC 75" debossed on the opposite tablet face.

PALBOCICLIB 100 mg TABLETS PFIZER

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

PALBOCICLIB 125 mg TABLETS PFIZER

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PALBOCICLIB PFIZER TABLETS is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination:

- with letrozole as initial endocrine-based therapy in postmenopausal women
- with fulvestrant in women with disease progression who have received prior endocrine therapy

4.2 Posology and method of administration

Treatment with PALBOCICLIB PFIZER TABLETS should be initiated and supervised by a medical practitioner experienced in the use of anticancer therapies.

Posology

The recommended starting dose of PALBOCICLIB PFIZER TABLETS is a 125 mg tablet taken orally once daily with or without food for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The treatment with PALBOCICLIB PFIZER TABLETS should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

When co-administered with PALBOCICLIB PFIZER TABLETS, the recommended dose of letrozole is 2,5 mg taken orally once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of letrozole. Treatment of pre/perimenopausal women with the combination of PALBOCICLIB PFIZER TABLETS plus letrozole should always be combined with a luteinizing hormone-releasing hormone (LHRH) agonist (see section 4.4).

When co-administered with PALBOCICLIB PFIZER TABLETS, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant. Prior to the start of treatment with the combination of PALBOCICLIB PFIZER TABLETS 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 modifications

Dose modification of PALBOCICLIB PFIZER TABLETS is recommended based on individual safety and tolerability.

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

Table 1. PALBOCICLIB PFIZER TABLETS Recommended dose modifications for adverse events

Dose Level	**Dose**
Recommended dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*
*If further dose reduction below 75 mg/day is required, discontinue the treatment.	

Complete blood count should be monitored prior to the start of PALBOCICLIB PFIZER TABLETS 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 ≥ 1 000/mm^3 and platelet counts of ≥ 50 000/mm^3 are recommended to receive PALBOCICLIB PFIZER TABLETS.

Table 2. PALBOCICLIB PFIZER TABLETS Dose modification and management – haematologic toxicities

CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3a	*Day 1 of cycle:* Withhold PALBOCICLIB PFIZER TABLETS, 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 PALBOCICLIB PFIZER TABLETS at the current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (> 1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of the subsequent cycles.
Grade 3 ANC[b] (< 1 000 to 500/mm^3) + fever ≥ 38,5 ºC and/or infection	At any time: Withhold PALBOCICLIB PFIZER TABLETS until recovery to Grade ≤ 2. Resume at the next lower dose.
Grade 4[a]	At any time: Withhold PALBOCICLIB PFIZER TABLETS until recovery to Grade ≤ 2. Resume at the next lower dose.

Grading according to CTCAE 4,0

ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.

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

[b] ANC: Grade 1: ANC < LLN – 1 500/mm^3; Grade 2: ANC 1 000 - < 1 500/mm^3; Grade 3: ANC 500 - < 1 000/mm^3; Grade 4: ANC < 500/mm^3.

Table 3. PALBOCICLIB PFIZER TABLETS Dose modification and management – non-haematologic toxicities

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

Grading according to CTCAE 4.0

CTCAE=Common Terminology Criteria for Adverse Events.

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

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

Special populations

Elderly population

No dose adjustment of PALBOCICLIB PFIZER TABLETS is necessary in patients ≥ 65 years of age (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of PALBOCICLIB PFIZER TABLETS is 75 mg once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days (see sections 4.1 and 5.2).

Renal impairment

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

Paediatric population

The safety and efficacy of PALBOCICLIB PFIZER TABLETS in children and adolescents ≤ 18 years of age have not been established. No data are available.

Method of administration

PALBOCICLIB PFIZER TABLETS is for oral use.

The tablets may be taken with or without food (see section 5.2). PALBOCICLIB PFIZER TABLETS should not be taken with grapefruit or grapefruit juice (see section 4.5).

PALBOCICLIB PFIZER TABLETS should be swallowed whole (should not be chewed, crushed, or split prior to swallowing). No 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 of PALBOCICLIB PFIZER TABLETS (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 PALBOCICLIB PFIZER TABLETS in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. PALBOCICLIB PFIZER TABLETS 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 PFIZER TABLETS have not been studied in patients with critical visceral disease (see section 5.1).

Haemotological disorders

Treatment 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 PALBOCICLIB PFIZER TABLETS when taken in combination with endocrine therapy.

Across clinical studies (PALOMA-1, PALOMA-2, PALOMA-3), 1,4 % of PALBOCICLIB PFIZER TABLETS -treated patients had ILD/pneumonitis of any grade, 0,1 % had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported (see section 4.8).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnoea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, PALBOCICLIB PFIZER TABLETS should be immediately interrupted and the patient should be evaluated. PALBOCICLIB PFIZER TABLETS should be permanently discontinued in patients with severe ILD or pneumonitis (see section 4.2).

Infections

Since PALBOCICLIB PFIZER TABLETS has myelosuppressive properties, it may predispose to infections.

Infections have been reported at a higher rate in patients treated with PALBOCICLIB PFIZER TABLETS in randomised clinical studies compared to patients treated in the respective comparator arm. Grade 3 and Grade 4 infections occurred respectively in 5,6 % and 0,9 % of patients treated with PALBOCICLIB PFIZER TABLETS 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).

Healthcare providers should inform patients to promptly report any episodes of fever.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with PALBOCICLIB PFIZER TABLETS (see section 4.8). Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

Hepatic impairment

PALBOCICLIB PFIZER TABLETS should be administered with caution to patients with moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment, with close monitoring of signs of toxicity (see sections 4.2 and 5.2).

Renal impairment

PALBOCICLIB PFIZER TABLETS should be administered 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 PFIZER TABLETS should be avoided. Co-administration should only be considered after careful evaluation of the potential benefits and risks. If co-administration with a strong CYP3A inhibitor is unavoidable, reduce the PALBOCICLIB PFIZER TABLETS dose to 75 mg once daily. When the strong inhibitor is discontinued, the dose of PALBOCICLIB PFIZER TABLETS should be increased (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).

Co-administration of CYP3A inducers may lead to decreased PALBOCICLIB PFIZER TABLETS exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of PALBOCICLIB PFIZER TABLETS with strong CYP3A4 inducers should be avoided. No dose adjustments are required for co-administration of PALBOCICLIB PFIZER TABLETS 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 PALBOCICLIB PFIZER TABLETS (see section 4.6).

4.5 Interaction with other medicines and other forms of interaction

PALBOCICLIB PFIZER TABLETS is primarily metabolised by CYP3A and sulphotransferase (SULT) enzyme SULT2A1. *In vivo*, PALBOCICLIB PFIZER TABLETS is a time-dependent inhibitor of CYP3A.

Effects of other medicines on the pharmacokinetics of PALBOCICLIB PFIZER TABLETS

Effect of CYP3A inhibitors

Co-administration of multiple 200 mg doses of itraconazole with a single 125 mg PALBOCICLIB PFIZER TABLETS dose increased PALBOCICLIB PFIZER TABLETS total exposure (AUC_{0-inf}) and the peak concentration (C_{max}) by approximately 87 % and 34 %, respectively, relative to a single 125 mg PALBOCICLIB PFIZER TABLETS 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

Co-administration of multiple 600 mg doses of rifampicin with a single 125 mg PALBOCICLIB PFIZER TABLETS dose decreased PALBOCICLIB PFIZER TABLETS AUC_{0-inf} and C_{max} by 85 % and 70 %, respectively, relative to a single 125 mg PALBOCICLIB PFIZER TABLETS 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).

Co-administration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg PALBOCICLIB PFIZER TABLETS dose decreased PALBOCICLIB PFIZER TABLETS $AUC_{0\text{-}inf}$ and C_{max} by 32 % and 11 %, respectively, relative to a single 125 mg PALBOCICLIB PFIZER TABLETS dose given alone. No dose adjustments are required for moderate CYP3A inducers (see section 4.4).

Effect of acid reducing medicines

Co-administration of multiple doses of the PPI rabeprazole with a single 125 mg PALBOCICLIB PFIZER TABLETS tablet under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg PALBOCICLIB PFIZER TABLETS tablet administered alone.

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.

Effects of PALBOCICLIB PFIZER TABLETS on the pharmacokinetics of other medicines

PALBOCICLIB PFIZER TABLETS is a weak, time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state. Co-administration of multiple doses of PALBOCICLIB PFIZER TABLETS with midazolam increased the midazolam $AUC_{0\text{-}inf}$ 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 co-administered with PALBOCICLIB PFIZER TABLETS as PALBOCICLIB PFIZER TABLETS may increase their exposure.

Drug-drug interaction between PALBOCICLIB PFIZER TABLETS 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 PFIZER TABLETS and letrozole when the two medicines were co-administered.

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 PFIZER TABLETS was co-administered with multiple doses of tamoxifen and when PALBOCICLIB PFIZER TABLETS was given alone.

Drug-drug interaction between PALBOCICLIB PFIZER TABLETS and fulvestrant

Data from a clinical study in patients with breast cancer showed that there was no clinically relevant interaction between PALBOCICLIB PFIZER TABLETS and fulvestrant when the two medicines were co-administered.

Drug-drug interaction between PALBOCICLIB PFIZER TABLETS and oral contraceptives

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

In vitro studies with transporters

Based on *in vitro* data, PALBOCICLIB PFIZER TABLETS is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of PALBOCICLIB PFIZER TABLETS with medicines 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 PFIZER TABLETS may inhibit the uptake transporter organic cationic transporter OCT1 and then may increase the exposure of medicine substrates of this transporter (e.g., metformin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Females of childbearing potential or their male partners who are receiving PALBOCICLIB PFIZER TABLETS, 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 PFIZER TABLETS in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

PALBOCICLIB PFIZER TABLETS is not recommended during pregnancy and in women of childbearing potential not using contraception (see section 5.3).

Breastfeeding

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

Fertility

There were no effects on oestrous cycle (female rats) or mating and fertility in rats in non-clinical reproductive studies. However, no clinical data have been obtained on fertility in human females.

Based on non-clinical safety findings in male reproductive tissues (seminiferous tubule degeneration in testis, epididymal hypospermia, lower sperm motility and density, and decreased prostate secretion) in non-clinical safety studies, male fertility may be compromised by treatment with PALBOCICLIB PFIZER TABLETS (see section 5.3). Thus, men should consider sperm preservation prior to beginning therapy with PALBOCICLIB PFIZER TABLETS.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of PALBOCICLIB PFIZER TABLETS 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 PFIZER TABLETS 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 PFIZER TABLETS were neutropenia, leukopenia, infections, anaemia, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased.

Dose reductions or dose modifications due to any adverse reaction occurred in 38,4 % of patients receiving PALBOCICLIB PFIZER TABLETS in randomised clinical studies regardless of the combination.

Permanent discontinuation due to an adverse reaction occurred in 5,2 % of patients receiving PALBOCICLIB PFIZER TABLETS in randomised clinical studies regardless of the combination.

Tabulated list of adverse reactions

Table 4 reports the adverse reactions from the pooled dataset of 3 randomised studies. The median duration of palbociclib treatment across the pooled dataset at the time of the final OS analysis was 14,8 months.

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

The adverse reactions are listed by system organ class and frequency category. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

System organ Preferred term[a] (PT)class Frequency	**Adverse Event**	All grades (%)	Grade 3 (%)	Grade 4 (%)

Infections and infestations				
Very common	Infections[b]	516 (59,2)	49 (5,6)	8 (0,9)
Blood and lymphatic system disorders				
Very common	Neutropenia[c]	716 (82,1)	500 (57,3)	97 (11,1)
	Leukopenia[d]	424 (48,6)	254 (29,1)	7 (0,8)
	Anaemia[e]	258 (29,6)	45 (5,2)	2 (0,2)
	Thrombocytopenia[f]	194 (22,2)	16 (1,8)	4 (0,5)
Common	Febrile neutropenia	12 (1,4)	10 (1,1)	2 (0,2)
Metabolism and nutrition disorders				
Very common	Decreased appetite	152 (17,4)	8 (0,9)	0 (0,0)
Nervous system disorders				
Common	Dysgeusia	79 (9,1)	0 (,0)	0 (0,0)
Eye disorders				
Common	Blurred vision	48 (5,5)	1 (0,1)	0 (0,0)
	Increased lacrimation	59 (6,8)	0 (0,0)	0 (0,0)
	Dry eye	36 (4,1)	0 (0,0)	0 (0,0)
Vascular disorders				
Common	Venous thromboembolism[i]	28 (3,2)	11 (1,3)	7 (0,8)
Respiratory, thoracic and mediastinal disorders				

Common	Epistaxis	77 (8,8)	0 (0,0)	0 (0,0)
Gastrointestinal disorders				
Very common	Stomatitis[g]	264 (30,3)	8 (0,9)	0 (0,0)
	Nausea	314 (36,0)	5 (0,6)	0 (0,0)
	Diarrhoea	238 (27,3)	9 (1.0)	0 (0,0)
	Vomiting	165 (18,9)	6 (0,7)	0 (0,0
Skin and subcutaneous tissue disorders				
Very common	Rash[h]	158 (18,1)	7 (0.8)	0 (0,0)
	Alopecia	234 (26,8)	N/A	N/A
	Dry skin	93 (10,7)	0 (0,0)	0 (0,0)
Common	Palmar-plantar erythrodysaesthesia syndrome	16 (1,8)	0 (0,0)	0 (0,0)
General disorders and administration site conditions				
Very common	Fatigue	362 (41,5)	23 (2,6)	2 (0,2)
	Asthenia	118 (13,5)	14 (1,6)	1 (0,1)
	Pyrexia	115 (13,2)	1 (0,1)	0 (0,0)
Investigations				
Very common	Increased ALT	92 (10,6)	18 (2,1)	1 (0,1)
	Increased AST	99 (11,4)	25 (2,9)	0 (0,0)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease;

N/n=number of patients; N/A=not applicable.

[a] PTs are listed according to MedDRA 17.1.

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

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

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

[e] Anaemia includes the following PTs: decreased anaemia, haemoglobin, decreased haematocrit.

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

[g] Stomatitis includes the following PTs: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

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

[i] Venous thromboembolism includes the following PTs: pulmonary embolism, embolism, deep vein thrombosis, peripheral embolism, thrombosis.

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

	PALBOCICLIB PFIZER TABLETS plus letrozole or fulvestrant			**Comparator arms***		
Laboratory abnor-malities	**All grades %**	**Grade 3 %**	**Grade %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Decreased WBC	97,4	41,8	1,0	26,2	0,2	0,2
Decreased neutrophils	95,6	57,5	11,7	17,0	0,9	0,6
Anaemia	80,1	5,6	N/A	42,1	2,3	N/A
Decreased platelets	65,2	1,8	0,5	13,2	0,2	0,0
Increased AST	55,5	3,9	0,0	43,3	2,1	0,0
Increased ALT	46,1	2,5	0,1	33,2	0,4	0,0

WBC=white blood cells; AST=aspartate aminotransferase; ALT=alanine aminotransferase; N=number of patients; N/A=not applicable.

Note: Laboratory results are graded according to the NCI CTCAE version 4.0 severity grade. * letrozole or fulvestrant

Description of selected adverse reactions

Overall, neutropenia of any grade was reported in 716 (82,1 %) patients receiving PALBOCICLIB PFIZER TABLETS regardless of the combination, with Grade 3 neutropenia being reported in 500 (57,3 %) patients, and Grade 4 neutropenia being reported in 97 (11,1 %) patients (see Table 4).

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

Febrile neutropenia has been reported in 0,9 % of patients receiving PALBOCICLIB PFIZER TABLETS in combination with fulvestrant and in 1,7 % of patients receiving PALBOCICLIB PFIZER TABLETS in combination with letrozole.

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

Post-marketing adverse events

System organ class	**Side effect**
Respiratory, thoracic and mediastinal disorders	ILD/pneumonitis[j]
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus
[j] ILD/PNEUMONITIS includes any reported Preferred Terms that are part of the Standardized MedDRA Query Interstitial Lung Disease (narrow).	

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. Health care providers are asked to

report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

In the event of a PALBOCICLIB PFIZER TABLETS 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 medicines, protein kinase inhibitors, ATC code: L01XE33.

Mechanism of action

Palbociclib is a highly selective, reversible, small molecule 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 efficacy against luminal breast cancers, particularly estrogen receptor (ER)-positive breast cancers.

In the cell lines tested, the loss of retinoblastoma (Rb) was associated with loss of palbociclib activity. However, in a follow-up study with fresh tumour samples, no relation between RB1 expression and tumour response was observed. Similarly, no relation was observed when studying the response to palbociclib in *in vivo* models with patient-derived xenografts (PDX models). Available clinical data are reported in the clinical efficacy and safety section (see below).

Cardiac electrophysiology

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

Clinical efficacy and safety

Summary of clinical studies

Randomised Phase 3 study of palbociclib in combination with letrozole (PALOMA-2)

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

A total of 666 postmenopausal women were randomised 2:1 to either the palbociclib plus letrozole arm or to the placebo plus letrozole arm and were stratified by site of disease (visceral, non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (*de novo* metastatic, ≤ 12 months from the end of adjuvant treatment to disease recurrence, > 12 months from the end of adjuvant treatment to disease recurrence), and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy, no prior hormonal therapy).

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

Patients were well matched for baseline demographics and disease characteristics between the palbociclib plus letrozole arm and the placebo plus letrozole arm. The median age of patients enrolled in this study was 62 years (range 28 - 89); 48,3 % of patients had received chemotherapy and 56,3 % had received antihormonal therapy in the neo-adjuvant and 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 and adjuvant setting. Most patients (97,4 %) had metastatic disease at baseline; 22,7 % of patients had bone only disease and 49,2 % of patients had visceral disease.

The primary endpoint of the study was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1,1 as assessed by investigator. Secondary efficacy endpoints included objective response (OR), duration of response (DOR), clinical benefit response (CBR), overall survival (OS), safety, EQ-5D scores and health-related quality of life (QoL) assessed using the FACT-B questionnaire.

At the data cut-off date of 26 February 2016, the study met its primary objective of improving PFS. The observed HR was 0,576 (95 % 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 cut-off date: 31 May 2017). A total of 405 PFS events were observed; 245 events (55,2 %) in the palbociclib plus letrozole arm and 160 (72,1 %) in the comparator arm respectively.

Table 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 (intent-to-treat population) - Efficacy results based on primary and updated cut-off dates

	Primary analysis (26 February 2016 cut-off)		Updated analysis (31 May 2017 cut-off)	
	Palbociclib plus letrozole (N=444)	Placebo plus letrozole (N=222)	Palbociclib 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)

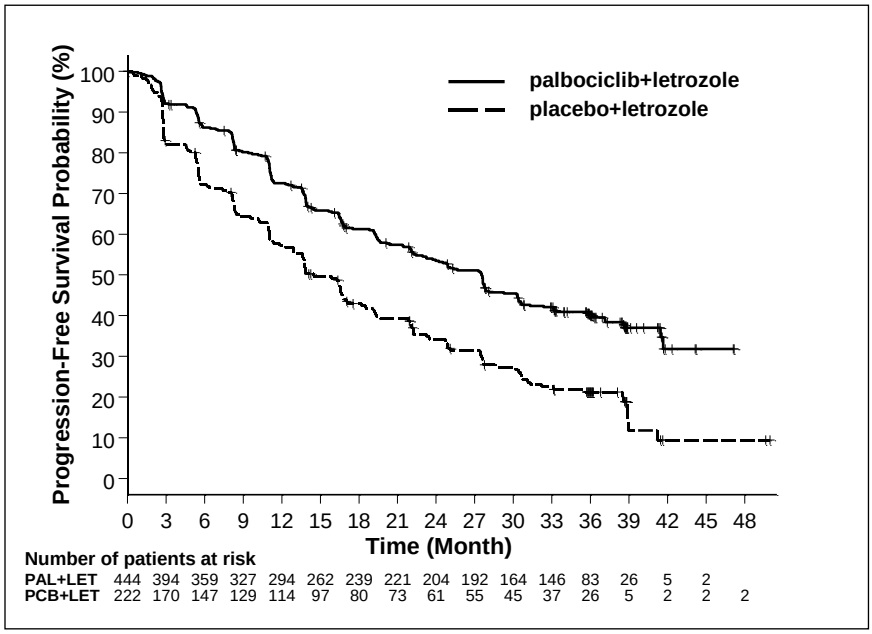
Median PFS [months (95 % CI)]	30,5 (27,4; NE)	19,3 (16,4; 30,6)	35,7 (27,7; 38,9)	19,5 (16,6; 26,6)
Hazard ratio (95 % CI) and 1-sided p-value	0,653 (0,505; 0,844), p=0,000532		0,611 (0,485; 0,769), p=0,000012	
OR* [% (95 % CI)]	46,4 (41,7; 51,2)	38,3 (31,9; 45,0)	47,5 (42,8; 52,3)	38,7 (32,3, 45,5)
OR* measurable disease [% (95 % CI)]	60,7 (55,2; 65,9)	49,1 (41,4; 56,9)	62,4 (57,0; 67,6)	49,7 (42,0; 57,4)
CBR* [% (95 % CI)]	85,8 (82,2; 88.9)	71,2 (64,7; 77,0)	85,6 (82,0; 88,7)	71,2 (64,7; 77,0)

N=number of patients; CI=confidence interval; NE=not estimable; OR=objective response; CBR=clinical benefit response; 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 cut-off 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)



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 favour 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 cut-off 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). For the 51 patients IHC negative for Rb expression, the difference between treatment arms was not statistically significant (HR of 0,868 [95 % CI: 0,424; 1,777], mPFS 23,2 versus 18,5 months) for the palbociclib plus letrozole arm versus the placebo plus letrozole arm, respectively.

Additional efficacy measures (OR and time to response [TTR]) assessed in the subgroups of patients with or without visceral disease based on the 31 May 2017 updated cut-off date are displayed in Table 6.

Table 6. Efficacy results in patients with visceral or non-visceral disease from PALOMA–2 study (intent to treat population; 31 May 2017 cut-off date)

	Visceral disease		Non-visceral disease	
	Palbociclib plus letrozole (N=214)	Placebo plus letrozole (N=110)	Palbociclib 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; OR=objective response 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 median time from randomisation to second subsequent therapy was 38,8 months in the palbociclib + letrozole arm and 28,8 months in the placebo + letrozole arm, HR 0,73 (95 % CI: 0,58; 0,91).

The results from the final OS analysis from the PALOMA-2 study are presented in Table 7. 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 7. PALOMA-2 (intent-to-treat population) – Final overall survival results

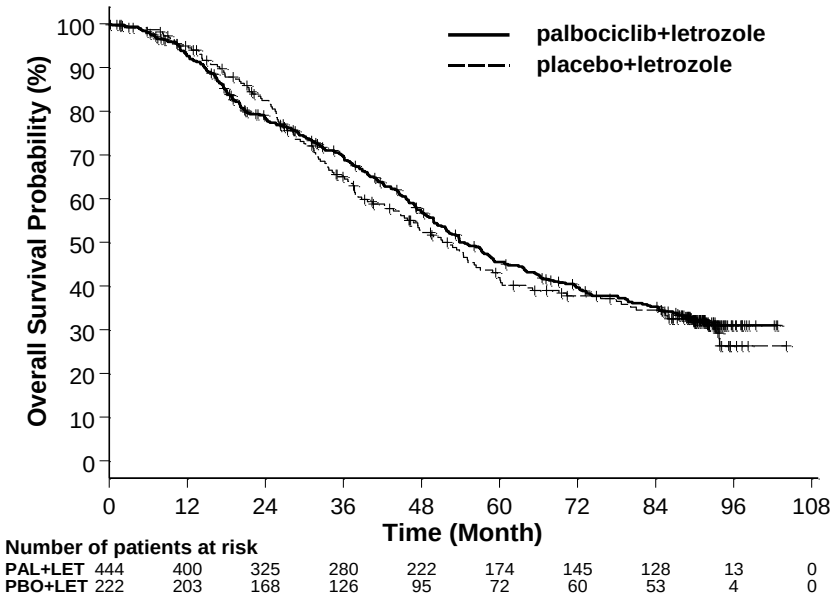
Final Overall Survival (OS) **(15 November 2021 Cutoff)**		
	Palbociclib **plus letrozole** **(N=444)**	**Placebo** **plus letrozole** **(N=222)**
Number of OS events (%)	287 (64,)	148 (66,7)
Number of subjects remaining in follow-up (%)	116 (26,1)	48 (21,6)
Median OS (months, 95 % CI)	53,8 (49,8; 59,2)	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 2249



Randomised, Phase 3 study of palbociclib in combination with fulvestrant (PALOMA-3)

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

A total of 521 pre/postmenopausal women whose disease had progressed during or within 12 months after completion of adjuvant endocrine therapy or during or within 1 month after prior endocrine therapy for advanced disease were randomised 2:1 to the palbociclib plus fulvestrant arm or the placebo plus fulvestrant arm and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. Crossover between treatment arms was not allowed.

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

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST version 1,1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, DOR, CBR, OS, safety, change in QoL, and Time to Deterioration (TTD). Patient-reported outcomes including Global QoL and pain were measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Breast Cancer Module (BR23) questionnaire.

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

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60 % of randomised patients). A 6,9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed; this result was not statistically significant at the prespecified significance level of 0,0235 (1-sided). In the 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 the PALOMA-3 study are presented in Table 8. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively.

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

	Updated analysis (23 October 2015 cut-off)	
	Palbociclib 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)
Final overall survival (OS) (13 April 2018 cut-off)		
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†*	

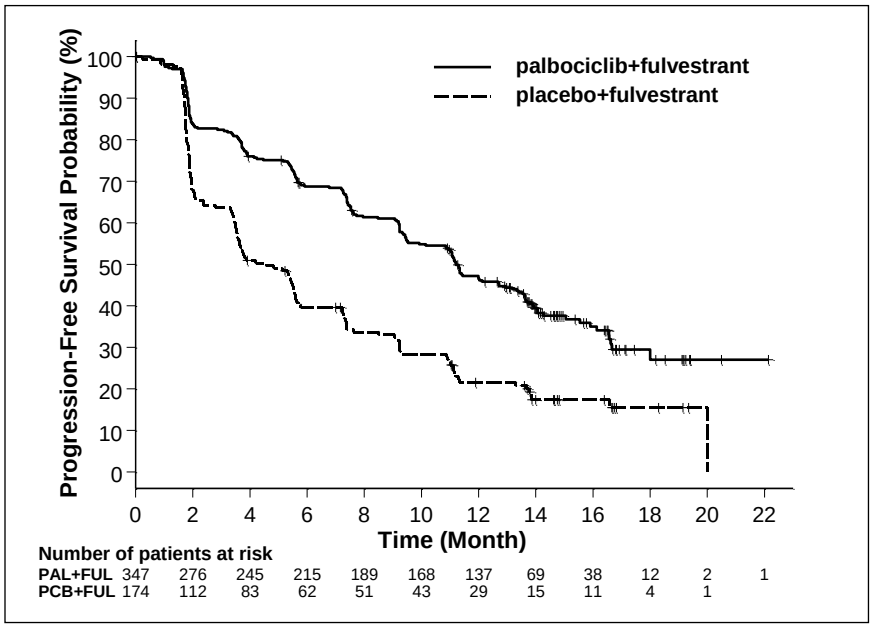
CBR=clinical benefit response; CI=confidence interval; N=number of patients; OR=objective response.

Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1,1.

* Not statistically significant.

† 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.

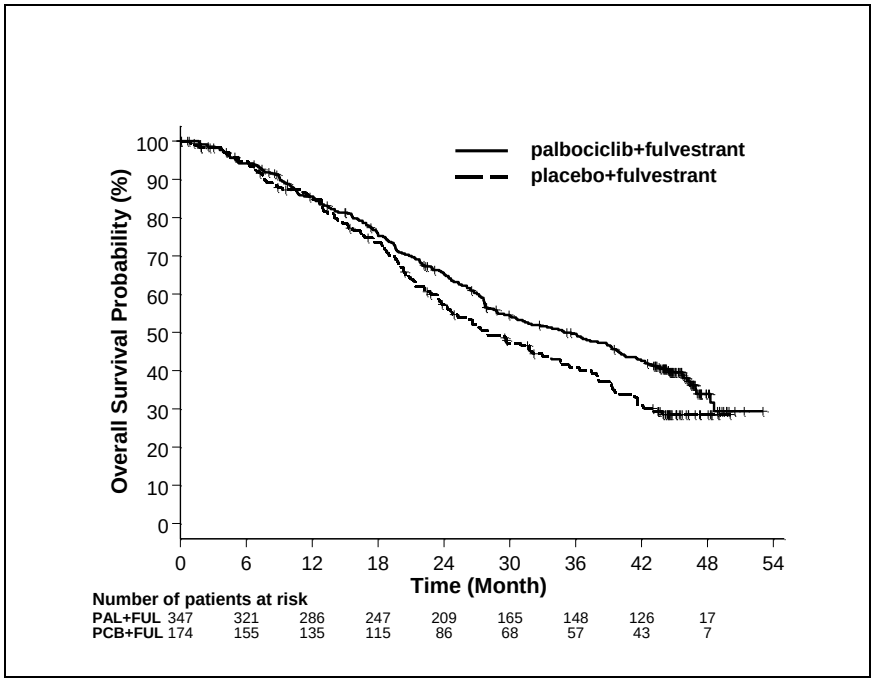
Figure 2. Kaplan-Meier plot of progression-free survival (investigator assessment, intent to treat population) – PALOMA-3 study (23 October 2015 cut-off)



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 3. Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA-3 study (13 April 2018 cut-off)



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

Additional efficacy measures (OR and TTR) assessed in the subgroups of patients with or without visceral disease are displayed in Table 8.

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

	Visceral disease		Non-visceral disease	
	Palbociclib plus fulvestrant (N=206)	Placebo plus fulvestrant (N=105)	Palbociclib 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 tumour response.				

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

TTD was prespecified as time between baseline and first occurrence of ≥ 10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8,0 months versus 2,8 months; HR of 0,64 [95 % CI: 0,49; 0,85]; $p < 0,001$).

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

The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46 %. In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increase proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulates with a median accumulation ratio of 2,4 (range 1,5 - 4,2).

Food effect

The AUC_{inf} and C_{max} of palbociclib increased by 22 % and 26 %, respectively, when palbociclib tablets were given with a high-fat, high-calorie meal (approximately 800 to 1 000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), and by 9 % and 10 %, respectively, when palbociclib 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 palbociclib tablets given under overnight fasted conditions. Based on these results, palbociclib tablets may be taken with or without food.

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 medicine-derived entity in plasma.

The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1,5 % of the administered dose in the excreta. The majority of the material was excreted as metabolites. In faeces, the sulphamic acid conjugate of palbociclib was the major medicine-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 a low potential to inhibit the activities of medicine transporters P-glycoprotein (P-gp, systemically), breast cancer resistance protein (BCRP, systemically), 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, sex, and body weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging from 37,9 to 123 kg), sex had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Hepatic impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic impairment indicate that palbociclib unbound $AUC_{0\text{-}inf}$ decreased 17 % in subjects with mild (Child-Pugh class A) hepatic impairment and increased by 34 % and 77 % in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Palbociclib f_uC_{max} increased by 7 %, 38 % and 72 % for mild (Child-Pugh class A), moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild (Child-Pugh class A) hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1,0 to 1,5 × ULN and any AST), mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of palbociclib, further supporting the findings from the dedicated hepatic impairment study.

Renal impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that palbociclib $AUC_{0\text{-}inf}$ increased by 39 %, 42 %, and 31 % with mild (60 mL/min/1,73m^2 ≤ CrCl < 90 mL/min/1,73m^2), moderate (30 mL/min/1,73m^2 ≤ CrCl < 60 mL/min/1,73m^2), and severe (CrCl < 30 mL/min/1,73m^2) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17 %, 12 %, and 15 % for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. In addition, based on a population pharmacokinetic analysis that included 183 patients where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring haemodialysis.

Paediatric population

Pharmacokinetic properties of palbociclib have not been evaluated in patients ≤ 18 years of age.

5.3 Pre-clinical 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 non-dosing 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 no-observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

Impairment of fertility

Palbociclib did not affect mating or fertility in female rats at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC) and no adverse effects were observed in female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 5 and 3 times human clinical exposure based on AUC, respectively).

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

Developmental toxicity

Palbociclib 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

Tablet core

Microcrystalline cellulose

Colloidal silicon dioxide

Crospovidone

Magnesium stearate

Succinic acid

Film-coating

Hypromellose (E464)

Titanium dioxide (E171)

Triacetin

Indigo carmine aluminum lake (E132)

Iron oxide red (E172) (75 mg and 125 mg tablets only)

Iron oxide yellow (E172) (100 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

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

6.5 Nature and content of container

PVC/OPA/Al/PVC/Al blister card containing 7 film-coated tablets (1 film-coated tablet per cell). Each carton contains 21 film-coated tablets (3 blister cards per carton).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (toll free South Africa)

8. REGISTRATION NUMBERS

PALBOCICLIB 75 mg TABLETS PFIZER: 56/26/1067.1064

PALBOCICLIB 100 mg TABLETS PFIZER: 56/26/1068.1065

PALBOCICLIB 125 mg TABLETS PFIZER: 56/26/1069.1066

9. DATE OF FIRST AUTHORISATION

04 March 2025

10. DATE OF REVISION OF THE TEXT

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PALBOCICLIB 75 mg TABLETS PFIZER: 2023/9.5.2/6499

PALBOCICLIB 100 mg TABLETS PFIZER: 2023/9.5.2/6500

PALBOCICLIB 125 mg TABLETS PFIZER: 2023/9.5.2/6501

Manufacturer: Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany