Palbociclib Tablets
Palbace®

1. GENERIC NAME

Palbociclib Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Palbociclib 75 mg/ 100 mg/ 125 mg

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

All strengths/presentation mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

75 mg/ 100 mg/ 125 mg film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

For Women:

Palbociclib is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:
- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.2).

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

For Men:

Palbociclib 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:

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- an aromatase inhibitor as initial endocrine-based therapy.
- fulvestrant in patients who have received prior therapy.

4.2 Posology and method of administration

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

Posology

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

When co-administered with palbociclib, the aromatase inhibitor should be administered according to the dose schedule reported in the Summary of Product Characteristics. Treatment of pre/perimenopausal women with the combination of palbociclib plus an aromatase inhibitor should always be combined with an LHRH agonist (see section 4.4).

When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the Summary of Product Characteristics of fulvestrant. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

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

For men treated with the combination of palbociclib plus aromatase inhibitor therapy, consider treatment with an LHRH agonist according to current clinical practice standards.

Dose adjustments

Dose modification of palbociclib 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. Palbociclib recommended dose modification 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 palbociclib 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.

Table 2. Palbociclib 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 Palbociclib, 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 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] (<1,000 to 500/mm^3) + Fever ≥38.5°C and/or infection	At any time: Withhold palbociclib until recovery to Grade ≤2. Resume at next lower dose.
Grade 4[a]	At any time: Withhold palbociclib 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 – 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 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.

Should be permanently discontinued in patients with severe interstitial lung disease (ILD)/pneumonitis (see section 4.4).

Special populations

Elderly

No dose adjustment of palbociclib is necessary in patients ≥ 65 years of age (see section 5.3).

Hepatic impairment

No dose adjustment of palbociclib 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 is 75 mg once daily on Schedule 3/1 (see sections 4.4 and 5.3).

Renal impairment

No dose adjustment of palbociclib is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥ 15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dose adjustment recommendation in this patient population (see sections 4.4 and 5.3).

Paediatric population

The safety and efficacy of palbociclib in children and adolescents < 18 years of age have not been established. No data are available.

Method of administration

Palbociclib is for oral use. The tablets may be taken with or without food (see section 5.3). Palbociclib should not be taken with grapefruit or grapefruit juice (see section 4.5).

Palbociclib 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 the active substance or to any of the excipients listed in section 2.

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 in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

Critical visceral disease

The efficacy and safety of palbociclib have not been studied in patients with critical visceral disease (see section 5.2).

Haematological disorders

Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed (see sections 4.2 and 4.8).

Interstitial lung disease/pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with palbociclib when taken in combination with endocrine therapy.

Across clinical studies (PALOMA-1, PALOMA-2, PALOMA-3), 1.4% of palbociclib-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 should be immediately interrupted and the patient should be evaluated. Palbociclib should be permanently discontinued in patients with severe ILD or pneumonitis (see section 4.2).

Infections

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

Infections have been reported at a higher rate in patients treated with palbociclib 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 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.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with PALBACE (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 should be administered with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity (see sections 4.2 and 5.3).

Renal impairment

Palbociclib 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 5.3).

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 palbociclib dose to 75 mg once daily. When the strong inhibitor is discontinued, the dose of palbociclib 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 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 co-administration of palbociclib with moderate CYP3A inducers (see section 4.5).

Women of childbearing potential or their partners

Women of childbearing potential or their male partners must use a highly effective method of contraception while taking palbociclib (see section 4.6).

4.5 Drugs interactions

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

Effects of other medicinal products on the pharmacokinetics of palbociclib

Effect of CYP3A inhibitors

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

The concomitant use of strong CYP3A inhibitors including, but not limited to: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole,

saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided (see sections 4.2 and 4.4).

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

Effect of CYP3A inducers

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

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

Coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by 32% and 11%, respectively, relative to a single 125 mg palbociclib dose given alone. No dose adjustments are required for moderate CYP3A inducers (see section 4.4).

Effect of acid reducing agents

Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg palbociclib tablet under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg palbociclib 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 on the pharmacokinetics of other medicinal products

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

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

Drug-drug interaction between palbociclib and oral contraceptives

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

In vitro studies with transporters

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

Drug-drug interaction between palbociclib and statins

Concomitant use of palbociclib with statins which are substrates of CYP3A4 and/or BCRP may increase the risk of rhabdomyolysis due to increased statin plasma concentration. Cases of rhabdomyolysis including fatal cases have been reported following coadministration of palbociclib with simvastatin or atorvastatin.

4.6 Use in special populations

Women of childbearing potential/Contraception in males and females

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

Pregnancy

There are no or limited amount of data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity (see section 6.1). Palbociclib is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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

Fertility

There were no effects on oestrous cycle (female rats) or mating and fertility in rats (male or female) in non-clinical reproductive studies. However, no clinical data have been obtained on fertility in humans. Based on male reproductive organ findings (seminiferous tubule degeneration in testis, epididymal hypospermia, lower sperm motility and density, and decreased prostate secretion) in non-clinical safety studies, male fertility may be compromised by treatment with palbociclib (see section 6.1). Thus, men may consider sperm preservation prior to beginning therapy with palbociclib.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

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

Permanent discontinuation due to an adverse reaction occurred in 5.2% of patients receiving palbociclib 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) and during post-marketing experience

System Organ Class Frequency Preferred term[a] (PT)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations			
Very common			
Infections[b]	516 (59.2)	49 (5.6)	8 (0.9)
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	716 (82.1)	500 (57.3)	97 (11.1)
Leukopenia[d]	424 (48.6)	254 (29.1)	7 (0.8)
Anaemia[e]	258 (29.6)	45 (5.2)	2 (0.2)
Thrombocytopenia[f]	194 (22.2)	16 (1.8)	4 (0.5)
Common			
Febrile neutropenia	12 (1.4)	10 (1.1)	2 (0.2)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	152 (17.4)	8 (0.9)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	79 (9.1)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	48 (5.5)	1 (0.1)	0 (0.0)
Lacrimation increased	59 (6.8)	0 (0.0)	0 (0.0)
Dry eye	36 (4.1)	0 (0.0)	0 (0.0)
Vascular disorders			
Common	28 (3.2)	11 (1.3)	7 (0.8)
Venous thromboembolism[j]			
Respiratory, thoracic and mediastinal disorders			
Common			
Epistaxis	77 (8.8)	0 (0.0)	0 (0.0)
ILD/pneumonitis[i]	12 (1.4)	1 (0.1)	0 (0.0)
Gastrointestinal disorders			
Very common			
Stomatitis[g]	264 (30.3)	8 (0.9)	0 (0.0)
Nausea	314 (36.0)	5 (0.6)	0 (0.0)
Diarrhoea	238 (27.3)	9 (1.0)	0 (0.0)
Vomiting	165 (18.9)	6 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	158 (18.1)	7 (0.8)	0 (0.0)
Alopecia	234 (26.8)	N/A	N/A

Dry skin	93 (10.7)	0 (0.0)	0 (0.0)
Common			
Palmar-plantar erythrodysaesthesia syndrome	16 (1.8)	0 (0.0)	0 (0.0)
Uncommon			
Cutaneous lupus erythematosus	1 (0.1)	0 (0.0)	0 (0.0)
Erythema multiforme	1 (0,1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	362 (41.5)	23 (2.6)	2 (0.2)
Asthenia	118 (13.5)	14 (1.6)	1 (0.1)
Pyrexia	115 (13.2)	1 (0.1)	0 (0.0)
Investigations			
Very common			
ALT increased	92 (10.6)	18 (2.1)	1 (0.1)
AST Increased	99 (11.4)	25 (2.9)	0 (0.0)
Common			
Blood creatinine increased	57 (6.5)	3 (0.3)	2 (0.2)

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

[a] PTs are listed according to MedDRA 17.1.

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

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

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

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

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

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

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

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

[j] 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 plus letrozole or fulvestrant			Comparator arms*		
Laboratory abnormalities	**All grades %**	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
WBC decreased	97.4	41.8	1.0	26.2	0.2	0.2
Neutrophils decreased	95.6	57.5	11.7	17.0	0.9	0.6
Blood creatinine increased	95.5	1.6	0.3	86.8	0.0	0.0
Anaemia	80.1	5.6	N/A	42.1	2.3	N/A
Platelets decreased	65.2	1.8	0.5	13.2	0.2	0.0
AST increased	55.5	3.9	0.0	43.3	2.1	0.0
ALT increased	46.1	2.5	0.1	33.2	0.4	0.0

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

Description of selected adverse reactions

Overall, neutropenia of any grade was reported in 716 (82.1%) patients receiving palbociclib 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 in combination with fulvestrant and in 1.7% of patients receiving palbociclib in combination with letrozole.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code:L01EF01.

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

5.2 Pharmacodynamic properties

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. 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 section 5.2).

Cardiac electrophysiology

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

Clinical efficacy and safety

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

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

A total of 666 postmenopausal women were randomised 2:1 to the palbociclib plus letrozole arm or placebo plus letrozole arm and were stratified by site of disease (visceral versus nonvisceral),

disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (*de novo* metastatic versus ≤12 months versus >12 months), and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy versus no prior hormonal therapy). Patients with advanced symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

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

Patients were well matched for baseline demographics and prognostic characteristics between the palbociclib plus letrozole arm and the placebo plus letrozole arm. The median age of patients enrolled in this study was 62 years (range 28-89), 48.3% of patients had received chemotherapy and 56.3% had received antihormonal therapy in the (neo)adjuvant setting prior to their diagnosis of advanced breast cancer while 37.2% of patients had received no prior systemic therapy in the (neo)adjuvant setting. The majority of patients (97.4%) had metastatic disease at baseline, 23.6% of patients had bone-only disease, and 49.2% of patients had visceral disease.

The primary endpoint of the study was progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (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 respectively.

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

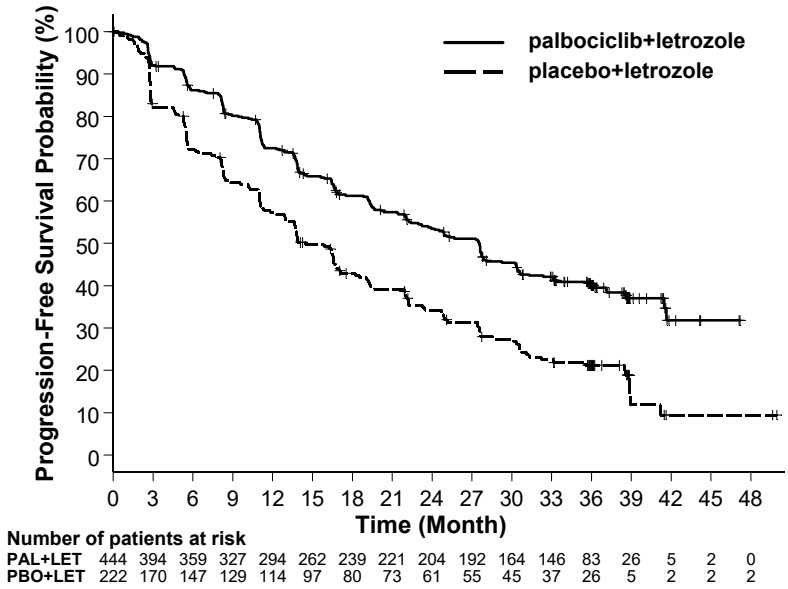
Table 6. PALOMA-2 (intent-to-treat population) - Efficacy results based on primary and updated cutoff dates

	Primary analysis (26 February 2016 cutoff)		Updated analysis (31 May 2017 cutoff)	
	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 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)



PAL=palbociclib; LET=letrozole; PBO=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 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). 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 sub-groups of patients with or without visceral disease based on the 31-May-2017 updated cutoff date are displayed in Table 7.

Table 7. Efficacy results in patients with visceral or non-visceral disease from PALOMA–2 study (intent-to-treat population; 31-May-2017 cutoff 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 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

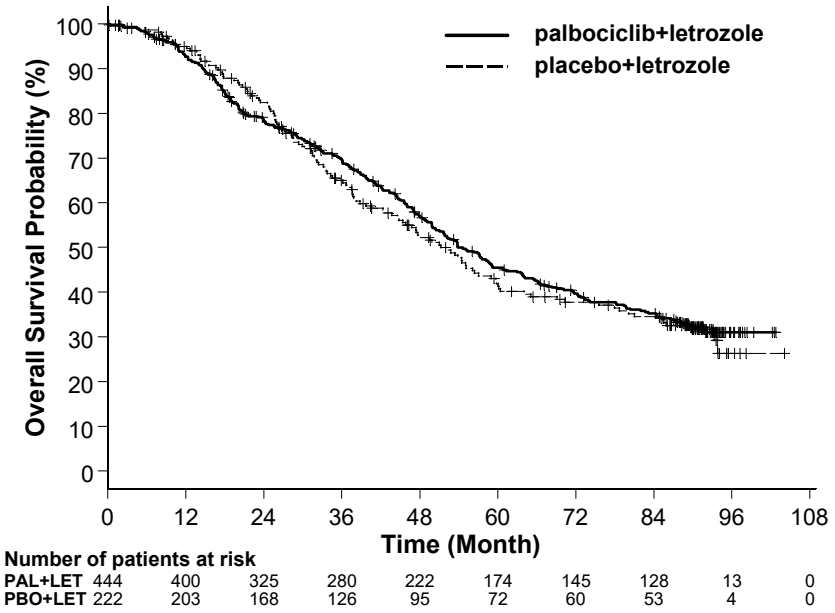
Final Overall Survival (OS) (15 November 2021 Cutoff)		
	Palbociclib plus letrozole (N=444)	**Placebo plus letrozole (N=222)**
Number of events (%)	273 (61.5)	132 (59.5)
Number of subjects remaining in follow-up (%)	112 (25.2)	43 (19.4)
Median OS (months [95% CI])	53.9 (49.8, 60.8)	51.2 (43.7, 58.9)
Hazard ratio (95% CI) and p-value[†]	0.956 (0.777, 1.177), p=0.6755[†*]	

CI=confidence interval.

[*] Not statistically significant.

[†] 2-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



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

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

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

A total of 521 pre/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy or on or within 1 month from prior endocrine therapy for advanced disease, were randomised 2:1 to palbociclib plus fulvestrant or placebo plus fulvestrant and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri- versus postmenopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

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

Patients were well matched for baseline demographics and prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. The median age of patients enrolled in this study was 57 years (range 29, 88). In each treatment arm the majority of patients were White, had documented sensitivity to prior hormonal therapy, and were postmenopausal. Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

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

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; the results crossed the prespecified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. A more mature update of efficacy data is reported in Table9.

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 PALOMA-3 study are presented in Table 9. The relevant Kaplan-Meier plots are shown in Figures 3 and 4, respectively.

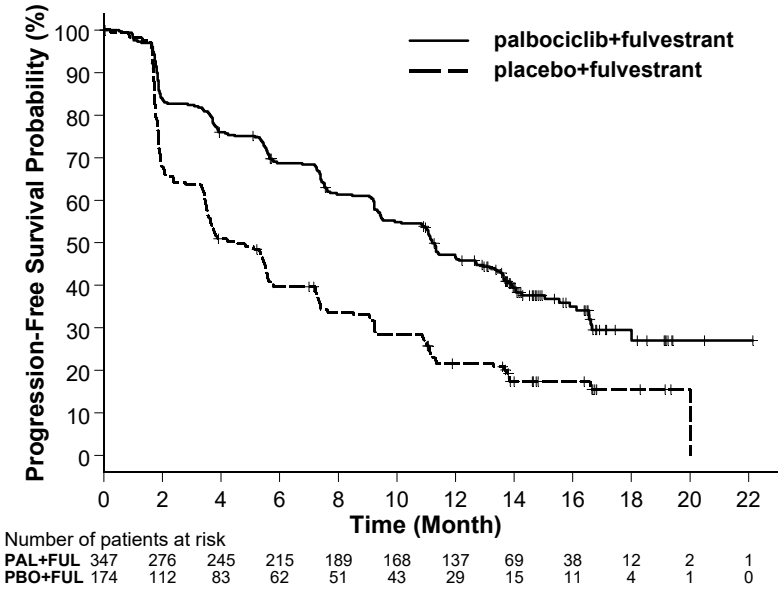
Table 9. Efficacy results – PALOMA-3 study (investigator assessment, intent-to-treat population)

	Updated analysis (23 October 2015 cutoff)	
	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 cutoff)		
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.

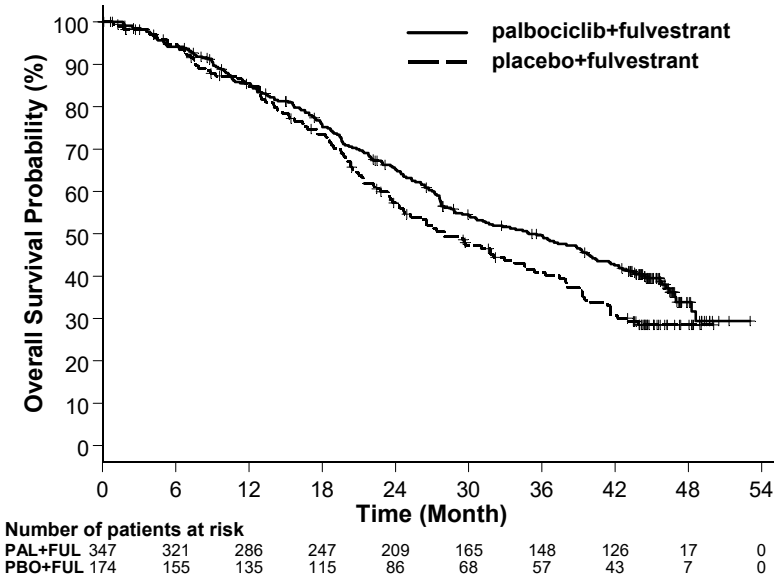
Figure 3. Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA-3 study (23 October 2015 cutoff)



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

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 10.

Table 10. 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 European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the fulvestrant only arm completed the questionnaire at baseline and at least 1 postbaseline visit.

Time-to-Deterioration was prespecified as time between baseline and first occurrence of ≥10 points increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a

symptom benefit by significantly delaying time-to-deterioration in pain symptom compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).

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

5.3 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 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

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

drug-derived entity in plasma.

The majority of the material was excreted as metabolites. In faeces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 25.8% of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulphotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63 L/h, and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{14}C] palbociclib, a median of 92% of the total administered radioactive dose was recovered in 15 days; faeces (74% of dose) was the major route of excretion, with 17% of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2% and 7% of the administered dose, respectively.

In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

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

Special populations

Age, gender, and body weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging from 38 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Paediatric population

Pharmacokinetics of palbociclib has not been evaluated in patients <18 years of age.

Hepatic impairment

Data from a pharmacokinetic study in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound AUC_{inf}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer, where 40 patients had mild hepatic impairment

based on National Cancer Institute (NCI) classification (total bilirubin ≤Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the pharmacokinetics of palbociclib.

Renal impairment

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

Ethnicity

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

6. NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

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

Carcinogenicity

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell 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.

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 non-clinical 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, respectively. 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.

7. DESCRIPTION

Palbociclib 75 mg tablets
round, light purple, film-coated tablets debossed with “pfizer” on one side and “pbc 75” on the other

side.

Palbociclib 100 mg tablets
oval, green, film-coated tablets debossed with “pfizer” on one side and “pbc 100” on the other side.

Palbociclib 125 mg tablets
oval, light purple, film-coated tablets debossed with “pfizer” on one side and “pbc 125” on the other side.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

36 months

8.3. Packaging information

Palbociclib is supplied in the following package configuration:

It contains 3 blister packs of 7 tablets each (21 tablets total)

8.4. Storage and handling instructions

Store below 30°C. Store in the original package in order to protect from moisture.

9. PATIENT COUNSELLING INFORMATION

Myelosuppression/Infection

- Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness, or any increased tendency to bleed and/or to bruise (see section 4.4 Special warnings and precautions for use).

Interstitial Lung Disease/Pneumonitis

- Advise patients to immediately report new or worsening respiratory symptoms(see section 4.4 Special warnings and precautions for use).

Drug Interactions

- Grapefruit may interact with PALBACE. Patients should not consume grapefruit products while on treatment with PALBACE.
- Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.
- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products (see section 4.5. Drug Interactions)

Dosing and Administration

- Inform patients that PALBACE tablets may be taken with or without food.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. PALBACE tablets should be swallowed whole (do not chew, crush, or split them prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.
- Pre/perimenopausal women treated with PALBACE should also be treated with LHRH agonists (see section 4.2. Posology and method of administration).

Pregnancy, Lactation, and Infertility

- Embryo-Fetal Toxicity
    - Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with PALBACE therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy (see section 4.4 Special warnings and precautions for use and section 4.6. Use in special populations).
    - Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PALBACE and for at least 3 months after the last dose (see section 4.6. Use in special populations)
- Lactation: Advise women not to breastfeed during treatment with PALBACE and for 3 weeks after the last dose (see section 4.6 Use in Specific Populations).
- Infertility: Inform males of reproductive potential that PALBACE may cause infertility and to consider sperm preservation before taking PALBACE (see section 4.6. Use in special populations)

10. DETAILS OF MANUFACTURER

M/s. Pfizer Manufacturing Deutschland GmbH Betriebsstatte Freiburg; Mooswaldallee 1 Freiburg - 79090 (Germany)

Imported and Marketed in India by:

Pfizer Products India Private Limited, The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

IMP/SND/20/000104 dated 23-Dec-2020 and subsequent approval IMP/SND/21/000062 dated 06-Aug-2021.

12. DATE OF REVISION

July 2024