Summary of Product Characteristics

PALBOCICLIB

(Palbociclib 75 mg, 100 mg and 125 mg Hard Capsules)

1 Name of the medicinal product

Palbociclib 75 mg hard capsules

Palbociclib 100 mg hard capsules

Palbociclib 125 mg hard capsule

2 Qualitative and quantitative composition

- Each hard capsule contains 75 mg of palbociclib.
- Each hard capsule contains 100 mg of palbociclib.
- Each hard capsule contains 125 mg of palbociclib.

Excipient(s) with known effect
Each hard capsule contains lactose (as lactose monohydrate). Each hard capsule contains less than 1 mmol (23 mg) sodium, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Hard capsule.

Palbociclib 75 mg hard capsules: yellow-coloured powder in a size "2" hard gelatin capsule with a white opaque body and a white opaque cap.

Palbociclib 100 mg hard capsules: yellow-coloured powder in a size "1" hard gelatin capsule with a Swedish-orange opaque body and a Swedish-orange opaque cap.

Palbociclib 125 mg hard capsules: yellow-coloured powder in a size "0" hard gelatin capsule with a white opaque body and a Swedish-orange opaque cap.

4 Clinical particulars

4.1 Therapeutic indications

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 5.1).

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

4.2 Posology and method of administration

Treatment with Palbociclib capsules 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. Treatment 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 its 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.

Dose adjustments

Dose modification 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 the dose-reduction schedules provided in Tables 1, 2 and 3 (see sections 4.4 and 4.8).

Table 1. Recommended dose modifications for adverse reactions

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

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

Complete blood count should be monitored prior to the start of 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) ≥ 1,000/mm³ and platelet counts ≥ 50,000/mm³ are recommended before receiving palbociclib.

Table 2. 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 the cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 guidance 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/mm³) + fever ≥ 38.5 °C and/or infection	At any time: withhold palbociclib until recovery to Grade ≤ 2. Resume at the next lower dose.
Grade 4[a]	At any time: withhold palbociclib 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] 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/mm³; Grade 2: ANC 1,000 – < 1,500/mm³; Grade 3: ANC 500 – < 1,000/mm³; Grade 4: ANC < 500/mm³.

Table 3. 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, or Grade ≤ 2 (if not considered a safety risk for the patient). Resume at the next lower dose.

Grading according to CTCAE 4.0.

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

Special populations

Elderly

No dose adjustment 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 is 75 mg once daily on Schedule 3/1 (see sections 4.4 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 dose adjustment recommendation in this patient population (see sections 4.4 and 5.2).

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. It should be taken with food, preferably a meal, to ensure consistent palbociclib exposure (see section 5.2). Palbociclib should not be taken with grapefruit or grapefruit juice (see section 4.5). The capsules should be swallowed whole and should not be chewed, crushed or opened prior to swallowing. No capsule should be ingested if it is broken, cracked or otherwise not intact.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Use of preparations containing St John's Wort (see section 4.5).

4.4 Special warnings and precautions for use

Pre/perimenopausal women

Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered 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 5.1).

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

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 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 with 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.

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 5.2).

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 5.2).

Concomitant treatment with inhibitors or inducers of CYP3A4
Strong inhibitors of CYP3A4 may lead to increased toxicity (see section 4.5). Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided, and 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 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 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 of 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).

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

Sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Palbociclib is primarily metabolised by CYP3A and the 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
Co-administration of multiple 200 mg doses of itraconazole with a single 125 mg palbociclib dose increased palbociclib total exposure (AUCinf) and peak concentration (Cmax) 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
Co-administration of multiple 600 mg doses of rifampicin with a single 125 mg palbociclib dose decreased palbociclib AUCinf and Cmax by 85% and 70%, respectively, relative to a single 125 mg palbociclib dose given alone. The concomitant use of strong CYP3A inducers including, but not limited to, carbamazepine, enzalutamide, phenytoin, rifampicin and St John's Wort should be avoided (see sections 4.3 and 4.4).

Co-administration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg palbociclib dose decreased palbociclib AUCinf and Cmax 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
Under fed conditions (intake of a moderate-fat meal), co-administration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single 125 mg dose of palbociclib decreased palbociclib Cmax by 41%, but had limited impact on AUCinf (13% decrease) compared with a single 125 mg dose administered alone. Under fasting conditions, co-administration of multiple doses of rabeprazole with a single 125 mg dose of palbociclib decreased palbociclib AUCinf and Cmax by 62% and 80%, respectively. Palbociclib should therefore be taken with food, preferably a meal (see sections 4.2 and 5.2). Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared with PPIs, no clinically relevant effect of H2-receptor antagonists or local antacids on palbociclib exposure is expected when palbociclib is taken with food.

Effects of palbociclib on the pharmacokinetics of other medicinal products
Palbociclib is a weak, time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state. Co-administration of multiple doses of palbociclib with midazolam increased the midazolam AUCinf and Cmax values by 61% and 37%, respectively, compared with administration of midazolam alone.

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

Interactions with endocrine therapies

Data from the drug-drug interaction evaluation portion of a clinical study in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the two medicinal products were co-administered. Data from a study in healthy male subjects indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when palbociclib was given alone. 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 studies of palbociclib with oral contraceptives have not been conducted (see section 4.6).

In vitro studies with transporters

Based on in vitro data, palbociclib is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of palbociclib with medicinal products that are substrates of P-gp (e.g. digoxin, dabigatran, colchicine) or BCRP (e.g. pravastatin, rosuvastatin, sulfasalazine) may increase their therapeutic effect and adverse reactions. Based on in vitro data, palbociclib may inhibit the uptake transporter organic cation transporter OCT1 and may therefore increase the exposure of medicinal product substrates of this transporter (e.g. metformin).

4.6 Fertility, pregnancy and lactation

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 data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Palbociclib is not recommended during pregnancy or 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 on 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 the 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 5.3). Men may therefore consider sperm preservation prior to beginning therapy with palbociclib.

4.7 Effects on ability to drive and use machines

Palbociclib has a 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 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

Adverse reactions from the pooled dataset of 3 randomised studies (N = 872) are listed below 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. Preferred terms are listed according to MedDRA 17.1.

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

System organ class	Frequency	Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations	Very common	Infections[b]	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)
	Very common	Leukopenia[d]	424 (48.6)	254 (29.1)	7 (0.8)
	Very common	Anaemia[e]	258 (29.6)	45 (5.2)	2 (0.2)
	Very common	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)
	Common	Lacrimation increased	59 (6.8)	0 (0.0)	0 (0.0)
	Common	Dry eye	36 (4.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	77 (8.8)	0 (0.0)	0 (0.0)
	Common	ILD/pneumonitis*	12 (1.4)	1 (0.1)	0 (0.0)
Gastrointestinal disorders	Very common	Stomatitis[g]	264 (30.3)	8 (0.9)	0 (0.0)
	Very common	Nausea	314 (36.0)	5 (0.6)	0 (0.0)
	Very common	Diarrhoea	238 (27.3)	9 (1.0)	0 (0.0)
	Very common	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)
	Very common	Alopecia	234 (26.8)	N/A	N/A

System organ class	Frequency	Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
	Very common	Dry skin	93 (10.7)	0 (0.0)	0 (0.0)
	Uncommon	Cutaneous lupus erythematosus*	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)
	Very common	Asthenia	118 (13.5)	14 (1.6)	1 (0.1)
	Very common	Pyrexia	115 (13.2)	1 (0.1)	0 (0.0)
Investigations	Very common	ALT increased	92 (10.6)	18 (2.1)	1 (0.1)
	Very common	AST increased	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. * Adverse reaction identified post-marketing.

[b] Infections includes all preferred terms that are part of the system organ class Infections and infestations. [c] Neutropenia includes: neutropenia, neutrophil count decreased. [d] Leukopenia includes: leukopenia, white blood cell count decreased. [e] Anaemia includes: anaemia, haemoglobin decreased, haematocrit decreased. [f] Thrombocytopenia includes: thrombocytopenia, platelet count decreased. [g] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis. [h] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

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

Laboratory abnormality	Palbociclib All grades %	Palbociclib Grade 3 %	Palbociclib Grade 4 %	Comparator* All grades %	Comparator* Grade 3 %	Comparator* 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
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. Laboratory results are graded according to 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 reported in 500 (57.3%) patients and Grade 4 neutropenia in 97 (11.1%) patients. 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 the 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 to the National Regulatory Authority.

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. There is no specific antidote.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors.

ATC code: L01EF01

Mechanism of action

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

Pharmacodynamic effects

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly oestrogen receptor-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.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms 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 oestrogen receptor-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 the placebo plus letrozole arm, stratified by site of disease (visceral versus non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (de novo metastatic versus ≤ 12 months versus > 12 months), and type of prior (neo)adjuvant anticancer therapies. Patients with advanced symptomatic visceral spread who were at risk of life-threatening complications in the short term were not eligible for enrolment. The median age of patients was 62 years (range 28–89); the majority (97.4%) had metastatic disease at baseline, 23.6% had bone-only disease and 49.2% had visceral disease.

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

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

	Palbociclib + letrozole (N = 444) primary	Placebo + letrozole (N = 222) primary	Palbociclib + letrozole (N = 444) updated	Placebo + letrozole (N = 222) updated
PFS events by investigator, n (%)	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); p-value	0.576 (0.463, 0.718); p < 0.000001		0.563 (0.461, 0.687); p < 0.000001	
PFS events by independent assessment, n (%)	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); 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)

CI = confidence interval; NE = not estimable; OR = objective response; CBR = clinical benefit response; PFS = progression-free survival. Primary analysis cut-off 26 February 2016; updated analysis cut-off 31 May 2017. Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.

A series of prespecified subgroup analyses showed a reduction in the risk of disease progression or death in favour of the palbociclib plus letrozole arm in all individual patient subgroups defined by stratification factors and baseline characteristics. Based on the 31 May 2017 cut-off, this reduction continued to be observed in patients with visceral metastases (HR 0.62 [95% CI: 0.47, 0.81]; median PFS 19.3 versus 12.3 months) and without visceral metastases (HR 0.50 [95% CI: 0.37, 0.67]; median PFS 35.9 versus 17.0 months), and in patients with bone-only disease (HR 0.41 [95% CI: 0.26, 0.63]; median PFS 36.2 versus 11.2 months) and without bone-only disease (HR 0.62 [95% CI: 0.50, 0.78]; median PFS 24.2 versus 14.5 months). A reduction in risk was also observed in 512 patients whose tumour tested positive for Rb protein expression by immunohistochemistry (HR 0.543 [95% CI: 0.433, 0.681]; median PFS 27.4 versus 13.7 months); for the 51 patients negative for Rb expression the difference between treatment arms was not statistically significant (HR 0.868 [95% CI: 0.424, 1.777]; median PFS 23.2 versus 18.5 months).

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

	Visceral: palbociclib + letrozole (N = 214)	Visceral: placebo + letrozole (N = 110)	Non-visceral: palbociclib + letrozole (N = 230)	Non-visceral: placebo + 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)

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 plus letrozole arm and 28.8 months in the placebo plus letrozole arm (HR 0.73 [95% CI: 0.58, 0.91]).

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 menopausal status, whose disease had progressed after prior endocrine therapy in the (neo)adjuvant or metastatic setting.

A total of 521 pre/peri- and postmenopausal women were randomised 2:1 to palbociclib plus fulvestrant or placebo plus fulvestrant, stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry, and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. The median age was 57 years (range 29–88); approximately 20% of patients were pre/perimenopausal, 60% had visceral metastases and 60% had received more than one prior hormonal regimen. The primary endpoint was investigator-assessed PFS according to RECIST 1.1; secondary endpoints included OR, CBR, overall survival (OS), safety and time to deterioration in pain.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis, crossing the prespecified Haybittle-Peto efficacy boundary. After a median follow-up 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 was observed in favour of the palbociclib plus fulvestrant arm, but this result was not statistically significant at the prespecified significance level. In the placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib or other CDK inhibitors as post-progression subsequent treatments.

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

	Palbociclib + fulvestrant (N = 347)	**Placebo + fulvestrant (N = 174)**
PFS events, n (%)	200 (57.6)	133 (76.4)
Median PFS, months (95% CI)	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio (95% CI); p-value	0.497 (0.398, 0.620); p < 0.000001	
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 OS events, n (%)	201 (57.9)	109 (62.6)
Median OS, months (95% CI)	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI); p-value	0.814 (0.644, 1.029); p = 0.0429 (not statistically significant)	

PFS updated analysis cut-off 23 October 2015; final OS cut-off 13 April 2018. Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.

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

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

	Visceral: palbociclib + fulvestrant (N = 206)	**Visceral: placebo + fulvestrant (N = 105)**	**Non-visceral: palbociclib + fulvestrant (N = 141)**	**Non-visceral: placebo + 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)

Patient-reported symptoms were assessed using the EORTC QLQ-C30 questionnaire and its breast cancer module (EORTC QLQ-BR23). Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying time to deterioration in pain symptoms compared with

placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR 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).

5.2 Pharmacokinetic properties

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

Absorption

The mean Cmax of palbociclib is generally observed between 6 and 12 hours following oral administration. The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the area under the curve (AUC) and Cmax increase proportionally with dose in general. Steady state was achieved within 8 days following repeated once-daily dosing. With repeated once-daily administration, palbociclib accumulates with a median accumulation ratio of 2.4 (range 1.5–4.2).

Food effect

Palbociclib absorption and exposure were very low in approximately 13% of the population under fasted conditions. Food intake increased palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Compared with palbociclib given under overnight fasted conditions, the AUCinf and Cmax of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after dosing. Food intake also significantly reduced the intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib should be taken with food (see section 4.2).

Distribution

Binding of palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence. The mean fraction unbound of palbociclib in human plasma in vivo increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib fraction unbound 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 [14C]palbociclib, the major primary metabolic pathways 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 indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination

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

route of excretion, with 17% of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2% and 7% of the administered dose, respectively.

In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8 and 3A4 at clinically relevant concentrations. In vitro evaluations indicate that palbociclib has low potential to inhibit the activities of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, and bile salt export pump (BSEP) at clinically relevant concentrations.

Special populations

Age, gender and body weight: based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, aged 22 to 89 years, body weight 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: the pharmacokinetics of palbociclib have 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 AUCinf) 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 unbound exposure (unbound Cmax) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively. In a population pharmacokinetic analysis including 183 patients with advanced cancer, 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 (AUCinf) 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 renal function (CrCl ≥ 90 ml/min). Peak exposure (Cmax) was increased by 17%, 12% and 15% for mild, moderate and severe renal impairment, respectively. In a population pharmacokinetic analysis, 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 AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese subjects compared with non-Asian subjects after a single oral dose. However, this finding was not reproduced consistently in subsequent studies in Japanese or Asian breast cancer patients after multiple dosing. Based on an analysis of the cumulative pharmacokinetic, safety and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary.

5.3 Preclinical safety data

The primary target organ findings of potential relevance to humans included haematolymphopoietic and male reproductive organ effects in rats and dogs in studies of 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 of ≥ 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 Cmax. 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 approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic findings 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 no observed effect level for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times human clinical exposure based on AUC) in males and 200 mg/kg/day (approximately 4 times human clinical exposure based on AUC) in females. 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. 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. 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 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 carry a 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-placental transfer have not been examined.

6 Pharmaceutical particulars

6.1 List of excipients

Capsule content

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

Capsule shell

- Gelatin
- Titanium dioxide
- Red iron oxide

Printing ink

- Shellac
- Dehydrated alcohol
- Isopropyl alcohol
- Butyl alcohol
- Propylene glycol
- Strong ammonia solution
- Black iron oxide
- Potassium hydroxide
- Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.

6.5 Nature and contents of container

PVC/Aclar blister packs with aluminium foil backing.

Pack sizes:

- 75 mg: packs of 7 and 14 capsules
- 100 mg: packs of 7 and 14 capsules
- 125 mg: packs of 7 and 10 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 Marketing authorisation holder

Glenmark Pharmaceuticals Ltd

B/2, Mahalaxmi Chambers

22, Bhulabhai Desai Road

Mumbai 400 026

India

8 Marketing authorisation number

CTD12622

9 Date of first authorisation/renewal of the authorisation

22.07.2026

10 Date of revision of the text

22.07.2026