℞ Palbociclib Capsules

Palboxen

Each hard gelatin capsule contains :
Palbociclib 75mg
Excipients q.s.
Approved colours used in empty capsule shell.

Each hard gelatin capsule contains :
Palbociclib 100mg
Excipients q.s.
Approved colours used in empty capsule shell.

Each hard gelatin capsule contains :
Palbociclib 125mg
Excipients q.s.
Approved colours used in empty capsule shell.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly ER-positive breast cancers. In the cell lines tested, the loss of retinoblastoma (Rb) was associated with loss of palbociclib activity. 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.

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.

Pharmacokinetic properties

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

Absorption

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

Food effect

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

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 fu 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 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 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 (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 (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 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.

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

DOSAGE AND 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 coadministered 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. When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice. Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Dose adjustments

Dose modification of 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

Table 1. PALBOCICLIB recommended dose modifications for adverse reactions

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

*If further dose reduction below 75 mg/day is required, discontinue the treatment.
Complete blood count should be monitored prior to the start of 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 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.
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 [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 ºC 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.
CTCAE=Common Terminology Criteria for Adverse Events.
PALBOCICLIB should be permanently discontinued in patients with severe interstitial lung disease (ILD)/pneumonitis.

Special population

Elderly

No dose adjustment of PALBOCICLIB is necessary in patients ≥ 65 years of age.

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.

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 .

Pediatric 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. Palbociclib should not be taken with grapefruit or grapefruit juice.
PALBOCICLIB capsules should be swallowed whole (should not be chewed, crushed, or opened prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Contraindications

Use of preparations containing St. John's Wort.

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.

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.

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% hadGrade3, 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.
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.

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. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate. 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.

Renal impairment

PALBOCICLIB should be administered with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity.

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. Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers.

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.

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.

Interaction with other medicinal products and other forms of interaction

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events.
PALBOCICLIB should be permanently discontinued in patients with severe interstitial lung disease (ILD)/pneumonitis.

Special population

Elderly

No dose adjustment of PALBOCICLIB is necessary in patients ≥ 65 years of age.

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.

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 .

Pediatric 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. Palbociclib should not be taken with grapefruit or grapefruit juice.
PALBOCICLIB capsules should be swallowed whole (should not be chewed, crushed, or opened prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Contraindications

Use of preparations containing St. John's Wort.

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.

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.

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% hadGrade3, 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.
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.

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. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate. 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.

Renal impairment
PALBOCICLIB should be administered with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity.

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. Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers.
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.

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.
Interaction with other medicinal products and other forms of interaction
Palbociclib is primarily metabolised by CYP3A and sulphotransferase (SULT) enzyme SULT2A1.
In vivo, palbociclib is a weak, time-dependent inhibitor of CYP3A.
Effects of other medicinal products on the pharmacokinetics of palbociclib
Effect of CYP3A inhibitors
Coadministration of multiple 200 mg doses of itraconazole with a single 125 mg palbociclib dose increased palbociclib total exposure (AUCinf[f] 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. 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 AUCinf [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. Coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg PALBOCICLIB dose decreased palbociclib AUCinf 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.
Effect of acid reducing agents
Under fed conditions (intake of a moderate-fat meal), coadministration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg PALBOCICLIB decreased palbociclib Cmax by 41%, but had limited impact on AUCinf (13% decrease) compared with a single dose of 125 mg PALBOCICLIB administered alone Under fasting conditions, the coadministration of multiple doses of the PPI rabeprazole with a single [dose of] 125 mg PALBOCICLIB decreased palbociclib AUCinf and C_{max} by 62% and 80%, respectively. Therefore, PALBOCICLIB should be taken with food, preferably a meal. Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, no clinically relevant effect of H2-receptor antagonists or local antacids on palbociclib exposure is expected when palbociclib is taken with food.
Effects of palbociclib on the pharmacokinetics of other medicinal products
Palbociclib is a weak, time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state. Coadministration of multiple doses of palbociclib with midazolam increased the midazolam AUCinf 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 coadministered.
Drug-drug interaction between palbociclib and oral contraceptives
DDI studies of palbociclib with oral contraceptives have not been conducted.

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

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. Pregnancy There are no or limited amount of data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity. PALBOCICLIB is 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 nonclinical safety studies, male fertility may be compromised by treatment with palbociclib. Thus, men may consider sperm preservation prior to beginning therapy with PALBOCICLIB.
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.

1.1 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 overall survival (OS) analysis was 14.8 months.
Table 5 reports the laboratory abnormalities observed in pooled datasets from 3 randomised studies.

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

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

System organ class Frequency Preferred term[a] (PT)	All Gradesn (%)	Grade 3n (%)	Grade 4n (%)
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] Leukopenia [d] Anaemia [e] Thrombocytopenia [f]	716 (82.1)	500 (57.3)	97 (11.1)
Common			
Febrile neutropenia	424 (48.6)	254 (29.1)	7 (0.8)
	258 (29.6)	45 (5.2)	2 (0.2)
	194 (22.2)	16 (1.8)	4 (0.5)
	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	48 (5.5)	1 (0.1)	0 (0.0)
	59 (6.8)	0 (0.0)	0 (0.0)
Vision blurred Lacrimation	36 (4.1)	0 (0.0)	0 (0.0)
increased Dryeye			
Respiratory, thoracic and mediastinal disorders			
Common	77 (8.8)	0 (0.0)	0 (0.0)
Epistaxis	12 (1.4)	1 (0.1)	0 (0.0)
ILD/pneumonitis [*,i]			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease; N/n=number of patients; N/A=not applicable.
* Adverse drug reaction identified post-marketing.
[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).

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

Gastrointestinal disorders			
Very common	264 (30.3)	8 (0.9)	0 (0.0)
Stomatitis [g]	314 (36.0)	5 (0.6)	0 (0.0)
Nausea	238 (27.3)	9 (1.0)	0 (0.0)
Diarrhoea	165 (18.9)	6 (0.7)	0 (0.0)
Vomiting			
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	158 (18.1)	7 (0.8)	0 (0.0)
Alopecia			
Dry skin			
Uncommon	234 (26.8)	N/A	N/A
Cutaneous lupus erythematosus *	93 (10.7)	0 (0.0)	0 (0.0)
	1 (0.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common	362 (41.5)	23 (2.6)	2 (0.2)
	118 (13.5)	14 (1.6)	1 (0.1)
Fatigue	115 (13.2)	1 (0.1)	0 (0.0)
Asthenia			
Pyrexia			
Investigations			
Very common	92 (10.6)	18 (2.1)	1 (0.1)
ALT increased AST Increased	99 (11.4)	25 (2.9)	0 (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

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.

Storage : Store below 30°C

Presentation: 21 Capsules are supplied in bottles

	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
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

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