Palbonix
Palbociclib

COMPOSITION

Palbonix 75 Capsule: Each capsule contains Palbociclib INN 75 mg

Palbonix 100 Capsule: Each capsule contains Palbociclib INN 100 mg

Palbonix 125 Capsule: Each capsule contains Palbociclib INN 125 mg

Therapeutic Class: Anti Cancer

CLINICAL PHARMACOLOGY

Mechanism of Action

Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. *In vitro*, Palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of Palbociclib and antiestrogens led to decreased retinoblastoma Rb protein phosphorylation resulting in reduced E2F expression and signaling, and increased growth arrest compared to treatment with each drug alone. *In vitro* treatment of ER-positive breast cancer cell lines with the combination of Palbociclib and antiestrogens leads to increased cell senescence, compared to each drug alone, which was sustained for up to 6 days following Palbociclib removal and was greater if antiestrogen treatment was continued. *In vitro* studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of Palbociclib and Letrozole increased the inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.

Pharmacodynamics

Cardiac Electrophysiology

The effect of Palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using timematched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib had no large effect on QTc (i.e., >20 ms) at 125 mg once daily (Schedule 3/1).

Pharmacokinetics

The pharmacokinetics (PK) of Palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

Absorption

The mean maximum observed concentration (C_{max}) of Palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration, T_{max}) 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 AUC and C_{max} increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, Palbociclib accumulated with a median accumulation ratio of 2.4 (range 1.5 to 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. Therefore, food intake reduced the intersubject variability of Palbociclib exposure, which supports administration of Palbociclib with food. Compared to Palbociclib given under overnight fasted conditions, the population average area under the concentration-time curve from zero to infinity (AUC_{inf}) and C_{max} of Palbociclib increased by 21% and 38%, respectively, when given with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), by 12% and 27%, respectively, when given with low-fat, low-calorie food (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate, and fat, respectively), and by 13% and 24%, respectively, when moderate-fat, standard calorie food (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively) was given 1 hour before and 2 hours after Palbociclib dosing.

Distribution

Binding of Palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The geometric mean apparent volume of distribution (Vz/F) was 2583 L with a coefficient of variation (CV) of 26%.

Metabolism

In vitro and in vivo studies indicated that Palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [14_C] Palbociclib to humans, the primary metabolic pathways for Palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23%). The major circulating metabolite was a glucuronide conjugate of Palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of Palbociclib was the major drug-related component, accounting for 26% of the administered dose. In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant 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 63.1 L/hr (29% CV), and the mean (± standard deviation) plasma elimination half-life was 29 (±5) hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [14_C] Palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. The majority of the material was excreted as metabolites.

Drug Interactions

Palbociclib is a substrate and weak inhibitor of CYP3A. It is also a moderate substrate of Pglycoprotein (P-gp) in vitro. Drug interactions were observed when Palbociclib was coadministered with a strong CYP3A inhibitor and a strong CYP3A inducer. The aqueous solubility of Palbociclib is pH-dependent. Drug interaction was observed when Palbociclib was coadministered with proton pump inhibitors (PPIs) under fasted conditions but was limited when Palbonix was coadministered with PPIs under fed conditions. Food intake reduced the variability of Palbociclib exposure. *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.

Agents that may increase Palbociclib plasma concentrations

CYP3A Inhibitors: Data from a study in 12 healthy subjects indicate that coadministration of multiple 200 mg daily doses of itraconazole with a single 125 mg Palbociclib dose increased Palbociclib total exposure (area under the curve, AUC_{inf}) and the peak exposure (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 are not limited to: Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Lopinavir, Nefazodone, Nelfinavir, Posaconazole, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazole, and Grapefruit or grapefruit juice, should be avoided.

Agents that may decrease Palbociclib plasma concentrations

CYP3A Inducers: Coadministration of a strong CYP3A inducer (Rifampin) decreased the plasma exposure of Palbociclib in healthy subjects by 85%. Avoid concomitant use of strong CYP3A inducers (e.g., Phenytoin, Rifampin, Carbamazepine, Enzalutamide, and St John's Wort)

Antacids: Data from a study in healthy subjects indicated that coadministration of a single 125 mg dose of Palbonix with multiple doses of the PPI Rabeprazole under fed conditions decreased Palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease) compared with a single dose of Palbonix administered alone. Given the reduced effect on gastric pH of H2 receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid reducing agents on Palbociclib exposure under fed conditions is expected to be minimal. Data from another study in healthy subjects indicated that coadministration of a single 125 mg dose of Palbociclib with multiple doses of the PPI Rabeprazole under fasted conditions decreased Palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with a single dose of Palbociclib administered alone.

Palbonix should be taken with food

CYP3A Substrates: Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In a study in 26 healthy subjects, coadministration of midazolam with multiple doses of Palbonix increased the midazolam AUC_{inf} and the C_{max} values by 61% and 37%, respectively, as compared with administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., Alfentanil, Cyclosporine, dihydroergotamine, Ergotamine, Everolimus, Fentanyl, Pimozide, Quinidine, Sirolimus and Tacrolimus) may need to be reduced as Palbonix may increase their exposure.

Letrozole: Data from a drug interaction portion of a clinical study in patients with breast cancer showed that there was no drug interaction between Palbociclib and Letrozole when the two drugs were coadministered

In vitro studies with transporters

In vitro evaluations indicated that Palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 at clinically relevant concentrations. *In vitro* studies with transporters In vitro evaluations indicated that Palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 at clinically relevant concentrations.

Drug-Food Interactions

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase Palbociclib plasma concentrations and should be avoided.

The effect of food on Palbociclib exposure was evaluated in healthy subjects. Compared to Palbociclib given under overnight fasted conditions, the AUC_{inf} and C_{max} of Palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food, and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after Palbonix dosing. In addition, food intake significantly reduced the inter-subject and intrasubject variability of Palbociclib exposure. Based on these results, Palbociclib should be taken with food.

Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (Hypericum perforatum) is an inducer of CYP3A4/5 that may decrease Palbociclib plasma concentrations and should be avoided.

Drug-Laboratory Interactions

Interactions between Palbociclib and laboratory tests have not been studied.

Drug-Lifestyle Interactions

Interactions between Palbociclib and lifestyle have not been studied.

INDICATION

Palbociclib is indicated for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
- fulvestrant in women with disease progression following endocrine therapy.

DOSAGE & ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of Palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food.

When coadministered with Palbociclib, the recommended dose of Letrozole is 2.5 mg taken once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of Letrozole.

When coadministered with Palbociclib, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Patients should be encouraged to take their dose of Palbociclib at approximately the same time each day.

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. Palbociclib capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination Palbociclib plus fulvestrant therapy should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards.

Dose Modification

The recommended dose modifications for adverse reactions are listed in Tables

Recommended Dose Modification for Adverse Reactions	
Dose Level	**Dose**
If further dose reduction below 75 mg/day is required, discontinue.	
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day

Monitor complete blood counts prior to the start of Palbociclib therapy and at the beginning of each cycle, as

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	*Day 1 of cycle:* Withhold Palbociclib , 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:* Continue Palbociclib at current dose to complete cycle. Repeat complete blood count on Day 22. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles.
Grade 3 neutropenia† with fever ≥38.5°C and/or infection	Withhold Palbociclib until recovery to Grade ≤2. Resume at the next lower dose.
Grade 4	Withhold Palbociclib until recovery to Grade ≤2. Resume at the next lower dose.

Dose Modification and Management – Non-Hematologic Toxicities	
CTCAE Grade	Dose Modifications
Grading according to CTCAE 4.0. CTCAE=Common Terminology Criteria for Adverse Events.	
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 nonhematologic toxicity (if persisting despite optimal 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.

USE IN SPECIAL POPULATION

Pregnancy

There are no adequate and well-controlled studies using Palbociclib in pregnant women. Palbociclib may cause fetal harm when administered to a pregnant woman. In animal studies, Palbociclib was shown to be fetotoxic in pregnant rats and rabbits. Palbociclib should not be used during pregnancy and is indicated for use in postmenopausal women. If Palbonix is used in women of childbearing potential, advise the patient to avoid becoming pregnant. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. If females of childbearing potential are receiving this drug they should use adequate contraceptive methods during therapy and for at least 21 days after completing therapy.

Lactation

It is not known whether Palbociclib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Palbonix, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the patient.

Pediatrics (< 18 years of age)

The safety and efficacy of Palbociclib in children and adolescents.

Geriatrics (65 years of age)

Population pharmacokinetic analysis was performed on data from 183 patients with cancer in an age range from 22 to 89 years. There was no clinically important difference in Palbociclib exposure in patients 65 years of age compared with patients.

Hepatic Impairment

Based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment, mild hepatic impairment had no effect on the exposure of Palbociclib. The pharmacokinetics of Palbociclib have not been studied in patients with moderate or severe hepatic impairment.

Renal Impairment

Based on a population pharmacokinetic analysis that included 183 patients, where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of Palbociclib. The pharmacokinetics of Palbociclib have not been studied in patients with severe renal impairment or requiring hemodialysis.

CONTRAINDICATION

None

WARNINGS AND PRECAUTION

General Effects on ability to drive and use machines No studies of the effects of Palbociclib on the ability to drive or operate machinery have been conducted. However, since fatigue and dizziness have been reported with the use of Palbociclib, patients should exercise caution when driving or operating machinery while taking Palbociclib.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted with Palbociclib.

Cardiovascular

Cardiac Electrophysiology In the in vivo cardiovascular safety pharmacology studies conducted in dogs, QTc interval prolongation was highly correlated with the plasma exposure to Palbociclib. An unbound plasma concentration of 67 ng/mL was associated with a 5 msec increase in QTc (approximately 4 times the unbound steady-state human Cmax) . The effect of Palbociclib on QTc was evaluated through a pharmacokinetic/pharmacodynamic analysis using data from 184 patients with advanced cancer. At the mean observed maximal steady-state Palbociclib concentration following a therapeutic schedule (e.g., 125 mg daily for 21 consecutive days followed by 7 days off to comprise a complete cycle of 28 days), the mean QTcS increase was 5.60 msec and the upper bound of the 1-sided 95% confidence interval (CI) was 8.72 msec. Clinically relevant QT prolongation due to Palbociclib is unlikely. A dedicated ECG substudy is ongoing.

Hematologic

Neutropenia Decreased neutrophil counts have been observed in clinical trials with Palbociclib. Neutropenia was the most frequently reported adverse reaction in the randomized Phase 2 study (PALOMA- 1), reported in 75% of patients treated with Palbociclib plus Letrozole compared to 5% of the Letrozole-only treated patients. A higher percentage of Grade 3 (48% versus 1%, respectively) and Grade 4 (6% versus 0%, respectively) neutropenia was reported in patients on the Palbociclib plus Letrozole arm compared with the Letrozole alone arm. Febrile neutropenia has been reported in approximately 1% of patients in the Palbonix clinical program, but no cases were observed in PALOMA-1. Median time to first episode of any grade neutropenia per laboratory data was 15 days (13-117 days) for any grade, Grade 2, and Grade 4 neutropenia, and 28 days for Grade 3 neutropenia. Median duration of Grade 3 or greater neutropenia was 7 days. In PALOMA-1, approximately half (48%) of the patients reported Grade 3 neutropenia, and most had their Palbonix dose reduced, interrupted, or their cycle delayed. Out of 5 patients with Grade 4 neutropenia, 2 patients permanently discontinued study treatment. Monitor complete blood count prior to the start of Palbonix therapy and at the beginning of each cycle, as well as on Day 14 of the first two cycles, and as clinically indicated. Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. For patients who experience Grade 3 neutropenia, consider repeating complete blood count monitoring one week later. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables.

Other Hematologic Parameters Decreases in hemoglobin, leukocytes, lymphocytes, and platelets were observed in PALOMA-1. Anemia and leukopenia were reported more frequently in patients treated with Palbociclib plus Letrozole (35% and 43%, respectively) compared to those treated with Letrozole alone (7% and 3%, respectively). Grade 3 leukopenia was reported in 19% of Palbociclib plus Letrozole patients. In PALOMA-1, anemia and leukopenia were usually managed with temporary Palbociclib discontinuation and/or dose reduction. Monitor complete blood count prior to the start of Palbociclib therapy, at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated.

Infections

Palbociclib may predispose patients to infections. Infections have been more frequently reported in patients treated with Palbociclib in clinical trials compared to those treated with Letrozole alone (55% vs. 34%, respectively, in Study PALOMA-1). Grade 3 or 4 infections occurred in 5% of patients treated with Palbociclib plus Letrozole and in no patients treated with Letrozole alone. Monitor patients for signs and symptoms of infection and treat as medically appropriate. Physicians should be aware of the increased risk of infection with Palbonix and should inform patients to promptly report any episodes of fever.

Respiratory

Pulmonary Embolism

Pulmonary embolism has been reported in 5% of patients treated with Palbociclib plus Letrozole compared with no cases in patients treated with Letrozole alone in Study PALOMA-1. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

ADVERSE REACTIONS

Most patients treated with Palbociclib experienced myelosuppressive effects with over half experiencing Grade 3 neutropenia at some point during treatment. Thrombocytopenia and anemia were less commonly observed. Myelosuppressive effects can be expected to occur from Cycle 1 forward.

OVERDOSAGE

There is no known antidote for Palbociclib. The treatment of overdose of Palbociclib should consist of general supportive measures.

PHARAMCEUTICAL INFORMATION

Storage Condition

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Palbonix 75 Capsule: Each commercial box contains 21 capsules in a bottle.

Palbonix 100 Capsule: Each commercial box contains 21 capsules in a bottle.

Palbonix 125 Capsule: Each commercial box contains 21 capsules in a bottle.

Only for Export

LF24401

Manufactured By
Beacon Pharmaceuticals Limited
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