Palker

Palbociclib

COMPOSITION

Palker 100 Capsule: Each capsule contains Palbociclib INN 100 mg

Palker 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, Tmax) 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 Cmax 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 (AUCinf) 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 Palker 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

Effect of CYP3A Inhibitors

Coadministration of a strong CYP3A inhibitor (Itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Lopinavir/Ritonavir, Nefazodone, Nelfinavir, Posaconazole, Ritonavir, Saquinavir, Telaprevir, Telithromycin, and Voriconazole). Avoid grapefruit or grapefruit juice during Palbociclib treatment. If coadministration of Palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of Palbociclib.

Agents that may decrease Palbociclib plasma concentrations

Effect of 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)

Drugs That May Have Their Plasma Concentrations Altered by Palbociclib

Coadministration of midazolam with multiple doses of Palbociclib increased the midazolam plasma exposure by 61%, in healthy subjects, compared to 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 Palbociclib may increase its exposure

Drug-Food Interactions

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

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.

When coadministered with Palbociclib, the recommended dose of Fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter.

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 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, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

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: If Grade 3 on Day 15, continue Palbociclib at 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 neutropenia with 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	At any time: Withhold Palbociclib until recovery to Grade ≤ 2 Resume at the next lower dose

Dose Modification and Management – Non-Hematologic Toxicities

CTCAE* Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-hematologic 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.

*CTCAE = Common Terminology Criteria for Adverse Events.

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.

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 Palbociclib, 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 pediatric patients have not been studied.

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.

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. 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.

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 Monitor patients for signs and symptoms of infection and treat as medically appropriate. Physicians should be aware of the increased risk of infection with Palbociclib 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. 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 dry place below 30°C and away from light. Keep out of the reach of children.

Presentation & Packaging

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

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

Manufactured by-
BEACON®
Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

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