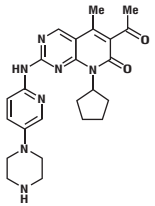
PALBOTIZ 75/100/125
PALBOCICLIB CAPSULES 75mg/ 100mg/ 125 mg

Rx only

COMPOSITION



PALBOTIZ 75

Palbociclib Capsules 75 mg

Each Capsules Contains	
Palbociclib	75 mg
Excipients	q.s

Colours: Approved colours used in capsule shell.

PALBOTIZ 100

Palbociclib Capsules 100 mg

Each Capsules Contains	
Palbociclib	100 mg
Excipients	q.s

Colours: Approved colours used in capsule shell.

PALBOTIZ 125

Palbociclib Capsules 125 mg

Each Capsules Contains	
Palbociclib	125 mg
Excipients	q.s

Colours: Approved colours used in capsule shell.

DESCRIPTION

Palbociclib capsules for oral administration contain 125 mg, 100 mg, or 75 mg of palbociclib, a kinase inhibitor. The molecular formula for palbociclib is $C_{24}H_{29}N_7O_2$. The molecular weight is 447.54 daltons. The chemical name is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one.

Palbociclib is a yellow to orange powder with pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.

Inactive ingredients: Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells. Approved colours used in capsule shell.

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 leads to decreased retinoblastoma protein (Rb) 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, which was sustained for up to 6 days following drug removal. In vivo 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 QTc interval was evaluated in 184 patients with advanced cancer. No large change (i.e., >20 ms) in the QTc interval was detected 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).

Pharmacokinetics

The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

Absorption: The mean 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 1.5–4.2).

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.

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 (26% CV).

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.

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.

Age, Gender, and Body Weight: Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 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.

Pediatric Population: Pharmacokinetics of Palbociclib have not been evaluated in patients <18 years of age.

INDICATIONS AND USAGE

Palbociclib is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

DOSAGE AND ADMINISTRATION

General Dosing Information: 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 in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle. 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. Palbociclib capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Dose Modification: 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.

Dose Modifications for use with Strong CYP3A Inhibitors: Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be co-administered a strong CYP3A inhibitor, reduce the Palbociclib dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the Palbociclib dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor

ADVERSE REACTIONS

The following topics are described below and elsewhere in the labeling:

- Neutropenia
- Infections
- Pulmonary Embolism

Clinical Studies Experience

Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The safety of Palbociclib (125 mg/day) plus letrozole (2.5 mg/day) versus letrozole alone was evaluated in Study 1. The data described below reflect exposure to Palbociclib in 83 out of 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of treatment in Study 1. The median duration of treatment for palbociclib was 13.8 months while the median duration of treatment for letrozole on the letrozole-alone arm was 7.6 months.

The most common adverse reactions (≥10%) of any grade reported in patients in the Palbociclib plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.

A/s. 182 x 100 mm Black

The most frequently reported serious adverse reactions in patients receiving Palbociclib plus letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%).

An increase incidence of infections events was observed in the palbociclib plus letrozole arm (55%) compared to the letrozole alone arm (34%). Febrile neutropenia events have been reported in the Palbociclib clinical program, although no cases were observed in Study 1. Grade ≥3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia.

Adverse drug reactions (≥10%) reported in patients who received IBRANCE plus letrozole or letrozole alone in Study 1 are listed in Table 1.

Table 1. Adverse Reactions* (≥10%) in Study 1

	Palbociclib + Letrozole (N=83)			Letrozole Alone (N=77)		
System Organ Class	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Adverse Reaction	%	%	%	%	%	%
Infections and infestations						
URI†	31	1	0	18	0	0
Blood and lymphatic system disorders						
Neutropenia	75	48	6	5	1	0
Leukopenia	43	19	0	3	0	0
Anemia	35	5	1	7	1	0
Thrombocytopenia	17	2	0	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	7	0	0
Nervous system disorders						
Peripheral neuropathy	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis§	25	0	0	7	1	0
Nausea	25	2	0	13	1	0
Diarrhea	21	4	0	10	0	0
Vomiting	15	0	0	4	1	0
Skin and subcutaneous tissue disorders						
Alopecia	22¶	N/A	N/A	3#	N/A	N/A
General disorders and administration site conditions						
Fatigue	41	2	2	23	1	0
Asthenia	13	2	0	4	0	0

N=number of subjects; N/A=not applicable; URI=Upper respiratory infection.

* Adverse Reaction rates reported in the table include all reported events regardless of causality.

† URI includes: Influenza, Influenza like illness, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection.

‡ Peripheral neuropathy includes: Neuropathy peripheral, Peripheral sensory neuropathy.

§ Stomatitis includes: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

¶ Grade 1 events - 21%; Grade 2 events - 1%.

\# Grade 1 events - 3%.

CONTRAINDICATIONS

None.

DRUG INTERACTIONS

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

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, verapamil, 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 and St.John's Wort).

Coadministration of moderate CYP3A inducers may also decrease the plasma exposure of Palbociclib. Avoid concomitant use of moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin).

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 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 Palbociclib may increase their exposure.

WARNINGS AND PRECAUTIONS

Neutropenia: Decreased neutrophil counts have been observed in clinical trials with Palbociclib. Grade 3 (57%) or 4 (5%) decreased neutrophil counts were reported in patients receiving Palbociclib plus letrozole in the randomized clinical trial (Study 1). Median time to first episode of any grade neutropenia per laboratory data was 15 days (13–117 days). Median duration of Grade ≥3 neutropenia was 7 days. Febrile neutropenia events have been reported in the Palbociclib clinical program, although no cases of febrile neutropenia have been observed in Study 1. Monitor complete blood count prior to starting Palbociclib 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.

Infections: Infections have been reported at a higher rate in patients treated with Palbociclib plus letrozole compared to patients treated with letrozole alone in Study 1. Grade 3 or 4 infections occurred in 5% of patients treated with Palbociclib plus letrozole whereas no patients treated with letrozole alone experienced a Grade 3 or 4 infection. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

Pulmonary Embolism: Pulmonary embolism has been reported at a higher rate in patients treated with Palbociclib plus letrozole (5%) compared with no cases in patients treated with letrozole alone in Study 1. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity: Based on findings in animals and mechanism of action, Palbociclib can cause fetal harm. Palbociclib caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were greater than or equal to 4 times the human clinical exposure based on area under the curve (AUC). Advise females of reproductive potential to use effective contraception during therapy with Palbociclib and for at least two weeks after the last dose.

OVERDOSAGE

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

HOW SUPPLIED

Palbociclib Capsules 75 mg, 100 mg & 125 mg supplied in a 21 capsules packed in a HDPE container.

STORAGE

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

SHELF LIFE

24 months

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited
Factory: Tukucha, Nala-1,
Banepa, Nepal.
Regd. Office: Maligoan-5,
Kathmandu, Nepal.