Composition: Each capsule contains Palbociclib INN 125 mg capsule.

Pharmacology:

Mechanism Of Action: Palbociclib is an inhibitor of Cyclin-dependent kinases (CDK) 4 and 6. cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. 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 (RB) protein phosphorylation resulting in reduced E2F expression and signaling, and increased growth arrest compared to treatment with each drug alone. Treatment of ER-positive breast cancer cell lines with the combination of Palbociclib and antiestrogens led 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 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.

Pharmacokinetic Properties:

Palbociclib presents a linear pharmacokinetic profile. **Absorption:** Its peak plasma concentration was observed 6-12 hours after oral administration. **Mean absolute bioavailability:** 46%. **Steady state:** within 8 days following repeated once daily dosing. **Plasma protein biniding:** 85%. The mean fraction unbound (FU) of Palbociclib in human plasma increased incrementally with worsening hepatic function. Mean apparent volume of distribution (VL/F) was 2583 l with a coefficient of variation (CV) of 26%. **Metabolism:** Palbociclib undergoes hepatic metabolism in humans. Palbociclib was the major circulating drug-derived entity in plasma (23%). CYP3A and SULT2A1 are mainly involved in the metabolism of Palbociclib. **Oral clearance:** 63.1 l/hr (29% CV). **Elimination half-life:** 29 (±5) hours in patients with advanced breast cancer. Radioactive dose was recovered in 15 days; a 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.

Indications:

Palbociclib is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- An aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or
- Fulvestrant in patients with disease progression following endocrine therapy.

Dosage & Administration:

Recommended Dose and Schedule

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. Patients should be encouraged to take their dose of Palbociclib at approximately the same time each day. For men treated with combination Palbociclib plus aromatase inhibitor therapy, consider treatment with an LHRH agonist according to current clinical practice standards.

Recommended Dose Modification for Adverse Reactions

Dose Level	Dose
Recommended Starting 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. Or, as directed by the registered physician.

Side Effects: Common side effects of Palbociclib include: WBC decreased, Neutrophils decreased, Neutropenia, Platelets decreased,infections, AST increased, ALT increased, Leukopenia, Fatigue, Nausea, Hair loss, Inflammation of the mouth and lips,

Palbo-125

Palbociclib INN 125 mg Capsule

DRUG INTERNATIONAL LTD.

Diarrhea, Anemia, Rash, Weakness/lethargy, Vomiting, Thrombocytopenia, Dry skin, Fever.

Contraindication:

None.

Drug Interaction: Palbociclib is primarily metabolized by CYP3A and Sulfotransferase (SULT) enzyme SULT2A1. Palbociclib is a time-dependent inhibitor of CYP3A.

Agents That May Increase Palbociclib Plasma Concentrations

Effect of CYP3A-Inhibitors

Effect of CYP3A Inhibitors

Coadministration of a strong CYP3A inhibitor (Itraconazole) increased the plasma exposure of Palbociclib in patients 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 patients, 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.

Precautions:

Neutropenia

Neutropenia was the most frequently reported adverse reaction. Monitor complete blood counts prior to starting Palbociclib therapy and at the beginning of each cycle, as well as on day 15 of the first 2 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. Febrile neutropenia has been reported in 1.8% of patients exposed to Palbociclib. One death due to neutropenic sepsis was observed. Physicians should inform patients to promptly report any episodes of fever.

Embryo-Fetal Toxicity

Palbociclib can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Palbociclib and for at least 3 weeks after the last dose.

Use In Pregnancy & Lactation: Palbociclib can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Use in Children:

Palbociclib is not indicated for use in children.

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

Storage: Store below 30°c in a dry place.

Packaging: Each box contains 21capsules in a blister pack.