PALBOXEN
Palbociclib INN

Everest

COMPOSITION
PALBOXEN capsule: Each capsule contains Palbociclib INN 125 mg.

INDICATION AND USAGE
Palbociclib is a kinase inhibitor 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.

PHARMACOLOGY
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.

DOSAGE AND ADMINISTRATION
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.

Administer the recommended dose of an aromatase inhibitor when given with Palbociclib. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

CONTRAINDICATION
• Hypersensitivity to the active substance
• Use of preparations containing St. John's Wort

WARNINGS AND PRECAUTION
Neutropenia
Neutropenia was the most frequently reported adverse reaction in Study 1 (PALOMA-2) with an incidence of 80% and Study 2 (PALOMA-3) with an incidence of 83%. A Grade ≥3 decrease in neutrophil counts was reported in 66% of patients receiving Palbociclib plus letrozole in Study 1 and 66% of patients receiving Palbociclib plus fulvestrant in Study 2. In Study 1 and 2, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥3 neutropenia was 7 days.

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 across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever.

Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including Palbociclib when taken in combination with endocrine therapy.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of Palbociclib-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4 and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt Palbociclib immediately and evaluate the patient. Permanently discontinue Palbociclib in patients with severe ILD or pneumonitis.

Embryo Fetal Toxicity
Based on findings from animal studies and its mechanism of action, Palbociclib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of Palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). 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.

SIDE EFFECTS
The following clinically significant adverse reactions are:
• Neutropenia
• ILD/Pneumonitis

DRUG INTERACTIONS
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) and the peak concentration (Cmax) 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.

Effect of CYP3A inducers
Coadministration of multiple 600 mg doses of rifampin with a single 125 mg Palbociclib dose decreased Palbociclib AUCinf and Cmax 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 Cmax 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 proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg Palbociclib decreased Palbociclib AUCinf and Cmax 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 Cmax 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).

USE IN SPECIFIC POPULATION
Women of childbearing potential or their partners
Women 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.

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.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
PALBOXEN capsule: Each HDPE container of Palbociclib contains 21 capsules (each capsule contains 125 mg Palbociclib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com

1901000065