PALBOTOR

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

Abbreviated Prescribing information for PALBOTOR

(Palbociclib Capsules 75mg/100mg/125 mg) [Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

Mechanism of Action: Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin Dl and CDK4/6 are downstream of signalling 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 G 1 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 phospho1ylation resulting in reduced E2F expression and signalling, 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 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 phospho1ylation, downstream signalling, and tumor growth compared to each drug alone.

Human bone marrow mononuclear cells treated with palbociclib in the presence or absence of an anti-estrogen in vitro did not become senescent and resumed proliferation following palbociclib withdrawal.

INDICATIONS: Palbociclib is a kinase inhibitor 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: As directed by the Physician. Tablets should be taken orally once daily.

CONTRAINDICATION: Hypersensitivity to the active substance or to any of the excipients.

WARNINGS & PRECAUTIONS: *Pre/perimenopausal women:* Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered Palbociclib in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. *Haematological disorders*: Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed. *Interstitial lung disease/pneumonitis*: Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with palbociclib when taken in combination with endocrine therapy. *Infections*: Since palbociclib has myelosuppressive properties, it may predispose patients to infections. *Hepatic impairment*: Palbociclib should be administered with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity. *Renal impairment*: Palbociclib should be administered with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity. *Concomitant treatment with inhibitors or inducers of CYP3A4:* Strong inhibitors of CYP3A4 may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. *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. *Lactose:* This medicinal product contains lactose. Patients with rare

hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product. *Sodium:* This medicinal product contains less than 1 mmol (23 mg) sodium per capsule, that is to say essentially 'sodium-free'.

DRUG INTERACTIONS: *Effect of CYP3A inhibitors:* 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 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%. *Effects of palbociclib on the pharmacokinetics of other medicinal products:* 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. *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 co-administered.

ADVERSE REACTIONS: : Infections, Neutropenia, Leukopenia, Anaemia and Thrombocytopenia, Febrile neutropenia, Decreased appetite, Dysgeusia, Vision blurred, Lacrimation increased and Dry eye, Epistaxis and ILD/pneumonitis, Stomatitis, Nausea, Diarrhoea and vomiting, Rash, Alopecia and Dry skin, Cutaneous lupus erythematosus, Fatigue, Asthenia and Pyrexia, ALT increased and AST increased

MARKETED BY:

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IN/PALBOTOR 75mg, 100mg, 125 mg/Dec-22/01/ABPI

(Additional information is available on request)