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

PALBOTOR

1. Generic Name:

Palbociclib Capsules 75mg/100mg/125 mg

2. Qualitative and quantitative composition:

Palbociclib Capsules 75 mg

Each hard gelatin capsule contains

Palbociclib…….….75 mg

Excipients……...q.s.

Approved colours used in capsule shell.

Palbociclib Capsules 100 mg

Each hard gelatin capsule contains

Palbociclib…….….100 mg

Excipients……...q.s.

Approved colours used in capsule shell.

Palbociclib Capsules 125 mg

Each hard gelatin capsule contains

Palbociclib…….….125 mg

Excipients……...q.s.

Approved colours used in capsule shell.

The excipients used are Microcrystalline Cellulose, Lactose Monohydrate, Sodium Starch Glycolate, Colloidal Silicone Dioxide, Magnesium Stearate, Hard Gelatin Capsule Shells.

3. Dosage form and strength:

Palbociclib Capsules 75 mg, 100 mg and 125 mg for oral use

4. Clinical particulars:

4.1 Therapeutic indication:

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.

4.2 Posology and method of administration

Treatment with Palbociclib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The treatment

with Palbociclib should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

When coadministered with palbociclib, the aromatase inhibitor should be administered according to the dose schedule reported in the Summary of Product Characteristics. Treatment of pre/perimenopausal women with the combination of palbociclib plus an aromatase inhibitor should always be combined with an LHRH agonist.

When coadministered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the Summary of Product Characteristics of fulvestrant. Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

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.

Dose adjustments

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 as per dose reduction schedules provided in Tables 1, 2, and 3.

Table 1. Palbociclib recommended dose modifications for adverse reactions

Dose Level	**Dose**
Recommended 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 the treatment.	

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

Complete blood count should be monitored 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, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle and as clinically indicated.

Absolute neutrophil counts (ANC) of ≥ 1,000/mm3 and platelet counts of ≥ 50,000/mm3 are recommended to receive palbociclib.

Table 2. Palbociclib dose modification and management – Haematological toxicities

CTCAE grade	**CTCAE grade**
Grade 1 or 2	Grade 1 or 2
Grade 3	Dat 1 of cycle:

	Withhold Palbociclib, until recovery to Grade ≤ 2, and 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 the 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 ANC[b] (<1,000 to 500/mm3) + Fever ≥ 38.5°C and/or infection	At any time: Withhold Palbociclib until recovery to Grade ≤ 2 Resume at next lower dose
Grade 4[a]	At any time Withhold Palbociclib until recovery to Grade ≤ 2. Resume at next lower dose
Grading according to CTCAE 4.0. ANC=absolute neutrophil counts; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lowerlimit of normal. [a] Table applies to all haematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections). [b] ANC: Grade 1: ANC < LLN – 1,500/mm3; Grade 2: ANC 1,000 - < 1,500/mm3; Grade 3: ANC 500 - < 1,000/mm3; Grade 4: ANC < 500/mm3.	

Table 3. Palbociclib dose modification and management – Non-haematological toxicities

CTCAE grade	**CTCAE grade**
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-haematological toxicity (if persisting despite 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.
Grade 4[a]	At any time Withhold Palbociclib until recovery to Grade ≤ 2. Resume at next lower dose
Grading according to CTCAE 4.0. CTCAE=Common Terminology Criteria for Adverse Events	

Palbociclib should be permanently discontinued in patients with severe interstitial lung disease (ILD)/pneumonitis.

Special populations

Elderly

No dose adjustment of Palbociclib is necessary in patients ≥ 65 years of age.

Hepatic impairment

No dose adjustment of Palbociclib is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of Palbociclib is 75 mg once daily on Schedule 3/1.

Renal impairment

No dose adjustment of Palbociclib is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥ 15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dose adjustment recommendation in this patient population.

Paediatric population

The safety and efficacy of Palbociclib in children and adolescents < 18 years of age have not been established. No data are available.

Method of administration

Palbociclib is for oral use. It should be taken with food, preferably a meal to ensure consistent palbociclib exposure. Palbociclib should not be taken with grapefruit or grapefruit juice.

Palbociclib capsules should be swallowed whole (should not be chewed, crushed, or opened prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

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. Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

Critical visceral disease

The efficacy and safety of palbociclib have not been studied in patients with critical visceral disease.

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.

Across clinical studies (PALOMA-1, PALOMA-2, PALOMA-3), 1.4% of palbociclib-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing

setting, with fatalities reported.

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnoea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, palbociclib should be immediately interrupted and the patient should be evaluated. Palbociclib should be permanently discontinued in patients with severe ILD or pneumonitis.

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.

Infections

Since palbociclib has myelosuppressive properties, it may predispose patients to infections.

Infections have been reported at a higher rate in patients treated with palbociclib in randomised clinical studies compared to patients treated in the respective comparator arm. Grade 3 and Grade 4 infections occurred respectively in 5.6% and 0.9% of patients treated with palbociclib in any combination.

Patients should be monitored for signs and symptoms of infection and treated as medically appropriate. Physicians should inform patients to promptly report any episodes of fever.

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. Coadministration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the palbociclib dose to 75 mg once daily. When the strong inhibitor is discontinued, the dose of palbociclib should be increased (after 3 5 half lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and

consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers.

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

Women of childbearing potential or their partners

Women of childbearing potential or their male partners must use a highly effective method of contraception while taking palbociclib.

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'.

4.5 Drug-Interaction:

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.

No dose adjustments are needed for mild and moderate CYP3A inhibitors.

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: arbamazepine, 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 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).

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential/Contraception in males and females

Females 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 contraceptio Based on findings from animal studies and its mechanism of action, palbociclib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. 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 AUC. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Animal Data

In a fertility and early embryonic development study in female rats, palbociclib was administered orally for 15 days before mating through to Day 7 of pregnancy, which did not cause embryo toxicity at doses up to 300 mg/kg/day with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of palbociclib up to 300 mg/kg/day and 20 mg/kg/day, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses ≥100 mg/kg/day in rats, there was an increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). At the maternally toxic dose of 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small phalanges in the forelimb. At 300 mg/kg/day in rats and 20 mg/kg/day in rabbits, the maternal systemic exposures were approximately 4 and 9 times the human exposure (AUC) at the recommended dose, respectively.

CDK4/6 double knockout mice have been reported to die in late stages of fetal development (gestation Day 14.5 until birth) due to severe anemia. However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, Palbociclib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with palbociclib.

Contraception

Females

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

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with palbociclib and for 3 months after the last dose. Infertility

Males

Based on animal studies, palbociclib may impair fertility in males of reproductive potential

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.

Pediatric Use

The safety and efficacy of palbociclib in pediatric patients have not been studied. Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), kidney (tubule vacuolation, chronic progressive nephropathy) and adipose tissue (atrophy) were identified in a 27 week repeat-dose toxicology study in rats that were immature at the beginning of the studies and were most prevalent in males at oral palbociclib doses ≥30 mg/kg/day (approximately 11 times the adult human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present with lower incidence and severity in a 15 week repeat-dose toxicology study in immature rats. Altered glucose metabolism or associated changes in the pancreas, eye, kidney and adipose tissue were not identified in a 27-week repeat-dose toxicology study in rats that were mature at the beginning of the study and in dogs in repeat-dose toxicology studies up to 39 weeks duration.

Toxicities in teeth independent of altered glucose metabolism were observed in rats. Administration of 100 mg/kg palbociclib for 27 weeks (approximately 15 times the adult human exposure [AUC] at the recommended dose) resulted in abnormalities in growing incisor teeth (discolored, ameloblast degeneration/necrosis, mononuclear cell infiltrate). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use

Of **444** patients who received palbociclib in Study 1, 181 patients (41%) were ≥65 years of age

and 48 patients (11%) were ≥75 years of age. Of **347** patients who received palbociclib in Study 2, 86 patients (25%) were ≥65 years of age and 27 patients (8%) were ≥75 years of age. No overall differences in safety or effectiveness of palbociclib were observed between these patients and younger patients.

Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of palbociclib is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Based on a pharmacokinetic trial in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUCINF) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound Cmax) increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function.

Review the Full Prescribing Information for the aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

Renal Impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment (CrCl >15 mL/min). Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUCINF) increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl <90 mL/min), moderate (30 mL/min ≤ CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (Cmax) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

4.7 Effects on ability to drive and use machines:

Palbociclib has minor influence on the ability to drive and use machines. However, palbociclib may cause fatigue and patients should exercise caution when driving or using machines.

4.8 Undesirable effects:

The most common (≥ 20%) adverse reactions of any grade reported in patients receiving palbociclib in randomised clinical studies were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, diarrhoea, alopecia and thrombocytopenia. The most common (≥ 2%) Grade ≥ 3 adverse reactions of palbociclib were neutropenia, leukopenia, infections, anaemia, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased.

Dose reductions or dose modifications due to any adverse reaction occurred in 38.4% of patients receiving palbociclib in randomised clinical

studies regardless of the combination.

Permanent discontinuation due to an adverse reaction occurred in 5.2% of patients receiving palbociclib in randomised clinical studies regardless of the combination.

The adverse reactions are listed by system organ class and frequency category. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in

order of decreasing seriousness. The following serious adverse reactions are described elsewhere in labeling:

Infections and infestations

Very Common: Infections

Blood and lymphatic system disorders

Very common: Neutropenia, Leukopenia, Anaemia and Thrombocytopenia

Common: Febrile neutropenia

Metabolism and nutrition disorders

Very Common: Decreased appetite

Nervous system disorders

Common: Dysgeusia

Eye disorders

Common: Vision blurred, Lacrimation increased and Dry eye

Respiratory, thoracic and mediastinal disorders

Common: Epistaxis and ILD/pneumonitis

Gastrointestinal disorders

Very Common: Stomatitis, Nausea, Diarrhoea and vomiting

Skin and subcutaneous tissue disorders

Very common: Rash, Alopecia and Dry skin

Uncommon: Cutaneous lupus erythematosus

General disorders and administration site conditions

Common: Fatigue, Asthenia and Pyrexia

Investigations

Very common: ALT increased and AST increased

Note: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease;

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

4.9 Overdose

In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and hematological (e.g., neutropenia) toxicity may occur and general supportive care should be provided.

5. Pharmacological properties:

5.1 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.

5.2 Pharmacodynamics properties

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly ER-positive breast cancers. In the cell lines tested, the loss of retinoblastoma (Rb) was associated with loss of palbociclib activity. However, in a follow-up study with fresh tumour samples, no relation between RB1 expression and tumour response was observed. Similarly, no relation was observed when studying the response to palbociclib in in vivo models with patient-derived xenografts (PDX models). Available clinical data are reported in the clinical efficacy and safety section.

Cardiac Electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched 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 for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

5.3 Pharmacokinetic properties

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 (Cmax) 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 Cmax 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 mean fraction unbound (fu) of palbociclib in human plasma in vivo increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib fu in human plasma in vivo with worsening renal function. 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 [14C] 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.

Excretion

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 [14C] 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.

Specific Populations

Age, gender, and body weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging from 38 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.

Paediatric population

Pharmacokinetics of palbociclib has not been evaluated in patients < 18 years of age.

Hepatic impairment

Data from a pharmacokinetic study in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound AUCinf) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound Cmax) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin ≤ Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) > ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the pharmacokinetics of palbociclib.

Renal impairment

Data from a pharmacokinetic study in subjects with varying degrees of renal function indicate that total palbociclib exposure (AUCinf) increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl < 90 mL/min), moderate (30 mL/min ≤ CrCl < 60 mL/min), and severe (CrCl < 30 mL/min) renal impairment, respectively, relative to subjects with normal (CrCl ≥ 90 mL/min) renal function. Peak palbociclib exposure (Cmax) was increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer, where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the pharmacokinetics of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring haemodialysis.

In a pharmacokinetic study in healthy volunteers, palbociclib AUCinf and Cmax values were 30% and 35% higher, respectively, in Japanese subjects compared with non-Asian subjects after a single oral dose. However, this finding was not reproduced consistently in subsequent studies in Japanese or Asian breast cancer patients after multiple dosing. Based on an analysis of the cumulative pharmacokinetic, safety, and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

The primary target organ findings of potential relevance to humans included haematolymphopoietic and male reproductive organ effects in rats and dogs in studies up to 39 weeks duration. Effects on glucose metabolism were associated with findings in the pancreas and secondary effects on eye, teeth, kidney, and adipose tissue in studies ≥ 15 weeks duration in rats only and bone changes were observed in rats only following 27 weeks of dosing. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. In addition, cardiovascular effects (QTc prolongation, decreased heart rate, and increased RR interval and systolic blood pressure) were identified in telemetered dogs at ≥ 4 times human clinical exposure based on Cmax. The reversibility of the effects on glucose

homeostasis, pancreas, eye, kidney, and bone was not established following a 12-week nondosing period, whereas partial to full reversal of effects on the haematolymphopoietic and male reproductive systems, teeth, and adipose tissue was observed.

Carcinogenicity

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell tumours in the central nervous system of males at 30 mg/kg/day; there were no neoplastic findings in female rats at any dose up to 200 mg/kg/day. The NOEL for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times the human clinical exposure based on AUC) and 200 mg/kg/day (approximately 4 times the human clinical exposure based on AUC) in males and females, respectively. The relevance of the male rat neoplastic finding to humans is unknown.

Genotoxicity

Palbociclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the in vitro human lymphocyte chromosome aberration assay.

Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells in vitro and in the bone marrow of male rats at doses ≥ 100 mg/kg/day. The exposure of animals at the no observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

Impairment of fertility

Palbociclib did not affect mating or fertility in female rats at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC), and no adverse effects were observed in female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 5 and 3 times human clinical exposure based on AUC, respectively). Palbociclib is considered to have the potential to impair reproductive function and fertility in male humans based on non-clinical findings in rats and dogs. Palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, and decreased secretion. These findings were observed in rats and/or dogs at exposures ≥ 9 times or subtherapeutic compared to human clinical exposure based on AUC, respectively. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week nondosing period, respectively. Despite these male reproductive organ findings, there were no effects on mating or fertility in male rats at projected exposure levels 13 times human clinical exposure based on AUC.

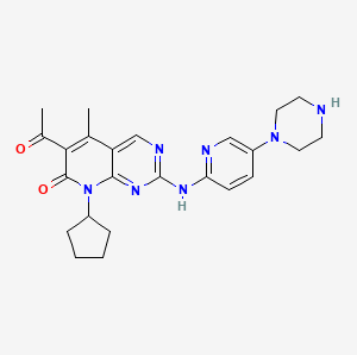
Developmental toxicity

Palbociclib is a reversible inhibitor of cyclin-dependent kinases 4 and 6, which are both involved in regulating the cell cycle. It may therefore have risk of foetal harm if used during pregnancy. Palbociclib was foetotoxic in pregnant animals. An increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra) at ≥ 100 mg/kg/day was observed in rats. Reduced foetal body weights were observed at a maternally toxic dose of 300 mg/kg/day in rats (3 times human clinical exposure based on AUC), and an increased incidence of skeletal variations, including small phalanges in the

forelimb was observed at a maternally toxic dose of 20 mg/kg/day in rabbits (4 times human clinical exposure based on AUC). Actual foetal exposure and cross-placenta transfer have not been examined.

7. Description

Palbociclib is 6-acetyl-8-cyclopentyl-5-methyl-2-[(5-piperazin-1-ylpyridin-2-yl) amino]pyrido[2,3-d]pyrimidin-7-one. The empirical formula is C24H29N7O2 and its molecular weight is 447.5 g/mol. The chemical structure of Palbociclib is:



PALBOTOR 75 is Black/Marron, "2" size, Hard gelatin capsules filled with yellow coloured granular powder.

PALBOTOR 100 is Marron/Yellow, "1" size, Hard gelatin capsules filled with yellow coloured granular powder.

PALBOTOR 125 is Black/Marron, "0" size, Hard gelatin capsules filled with yellow coloured granular powder.

The excipients used are Microcrystalline Cellulose, Lactose Monohydrate, Sodium Starch Glycolate, Colloidal Silicone Dioxide, Magnesium Stearate, Hard Gelatin Capsule Shells.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

PALBOTOR is available in bottle pack of 21 capsules

8.4 Storage and handing instructions

Store below 30°C.

Keep container tightly closed.

Dispense in original container.

Do not use if seal over bottle opening is broken or missing.

Keep away from the reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

PALBOTOR

PALBOTOR Each film coated tablet

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What PALBOTORis and what it is used for

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.

9.2 What you need to know before you take PALBOTOR

Do not take PALBOTOR

- If you are allergic to palbociclib or any of the other ingredients of this medicine.
- Use of preparations containing St. John's Wort, a herbal product used to treat mild depression and anxiety, should be avoided while you are taking PALBOTOR.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PALBOTOR.

PALBOTOR may reduce the number of your white blood cells and weaken your immune system. Therefore, you may be at greater risk of getting an infection while you are taking PALBOTOR.

Tell your doctor, pharmacist or nurse if you experience signs or symptoms of an infection, such as chills or fever.

You will have regular blood tests during treatment to check whether PALBOTOR affects your blood cells (white blood cells, red blood cells, and platelets).

PALBOTOR may cause severe or life-threatening inflammation of the lungs during treatment that can lead to death. Tell your healthcare provider right away if you have any new or worsening symptoms including:

• Difficulty breathing or shortness of breath

• Dry cough

• Chest pain

Children and adolescents

PALBOTOR is not to be used in children or adolescents (under 18 years of age).

Other medicines and PALBOTOR

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. PALBOTOR may affect the way some other medicines work.

In particular, the following may increase the risk of side effects with PALBOTOR:

• Lopinavir, indinavir, nelfinavir, ritonavir, telaprevir, and saquinavir used to treat HIV infection/AIDS.

• Clarithromycin and telithromycin antibiotics used to treat bacterial infections.

• Voriconazole, itraconazole, ketoconazole, and posaconazole used to treat fungal infections.

• Nefazodone used to treat depression.

The following medicines may have increased risk of side effects when given with PALBOTOR:

• Quinidine generally used to treat heart rhythm problems.

• Colchicine used to treat gout.

• Pravastatin and rosuvastatin used to treat high cholesterol levels.

• Sulfasalazine used to treat rheumatoid arthritis.

• Alfentanil used for anaesthesia in surgery; fentanyl used in pre-procedures as a pain reliever as well as an anaesthetic.

• Cyclosporine, everolimus, tacrolimus, and sirolimus used in organ transplantation to prevent rejection.

• Dihydroergotamine and ergotamine used to treat migraine.

• Pimozide used to treat schizophrenia and chronic psychosis.

The following medicines may reduce the effectiveness of PALBOTOR:

• Carbamazepine and phenytoin, used to stop seizures or fits.

• Enzalutamide to treat prostate cancer.

• Rifampin used to treat tuberculosis (TB).

• St. John’s Wort, a herbal product used to treat mild depression and anxiety.

PALBOTOR with food and drink

Avoid grapefruit and grapefruit juice while you are taking PALBOTOR as it may increase the side effects of PALBOTOR.

Pregnancy and breast-feeding and fertility

You should not use PALBOTOR if you are pregnant.

You should avoid becoming pregnant while taking PALBOTOR.

Discuss contraception with your doctor if there is any possibility that you or your partner may

become pregnant.

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Women of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods (e.g., double-barrier contraception such as condom and diaphragm). These methods should be used during therapy and for at least 3 weeks after completing therapy for females and for at least 14 weeks for males.

Breast-feeding

You should not breast-feed while taking PALBOTOR. It is not known if PALBOTOR is excreted in breast milk.

Fertility

Palbociclib may decrease fertility in men.

Therefore, men may consider sperm preservation before taking PALBOTOR.

Driving and using machines

Tiredness is a very common side effect of PALBOTOR. If you feel unusually tired, take special care when driving or using machines.

PALBOTOR contains lactose and sodium

This medicine contains lactose (found in milk or dairy products). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say it is essentially 'sodium-free'.

9.3 How to take PALBOTOR

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take PALBOTOR once a day at about the same time every day with food, preferably a meal.

Swallow the capsule whole with a glass of water. Do not chew or crush the capsules. Do not open the capsules.

If you take more PALBOTOR

If you have taken too much PALBOTOR, see a doctor or go to a hospital immediately. Urgent treatment may be necessary.

If you forget to take PALBOTOR

If you miss a dose or vomit, take your next dose as scheduled. Do not take a double dose to make up for the forgotten capsules.

If you stop taking PALBOTOR

Do not stop taking PALBOTOR unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you have any of these symptoms:

• fever, chills, weakness, shortness of breath, bleeding, or easy bruising which could be a sign of a serious blood disorder.

• difficulty breathing, dry cough or chest pain which could be a sign of inflammation of the lungs.

Other side effects with PALBOTOR may include:

Very Common side effects:

- Infections
- Reduction in white blood cells, red blood cells, and blood platelets
- Feeling of tiredness
- Decreased appetite
- Inflammation of the mouth and lips (stomatitis), nausea, vomiting, diarrhoea
- Rash
- Hair loss
- Weakness
- Fever
- Abnormalities in liver blood tests
- Dry skin

Common side effects:

- Fever with a drop in the white blood cell count (febrile neutropenia)
- Blurred vision, increased tearing, dry eye
- Alteration in taste (dysgeusia)
- Nosebleed

Uncommon side effects:

Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints and fever (Cutaneous Lupus Erythematosus [CLE]).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

9.5 How to store PALBOTOR

Store below 30ºC.

Keep out of the reach of children.

9.6 Contents of the pack and other information

The active substance is Palbociclib. Each Palbociclib Capsules contains 75, 100 or 125 mg Palbociclib

PALBOTOR is available in bottle pack of 21 capsules

10. Details of manufacturer

Hetero Labs Ltd. (Unit – I)

Village: Kalyanpur, Chakkan Road,

Tehsil: Baddi, Distt.: Solan,

Himachal Pradesh – 173 205.

11. Details of permission or license number with date

MNB/06/328 issued on 26.09.2022

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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