SUMMARY PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

Brand Name

PALBOCARE 125

Generic Name

PALBOCICLIB CAPSULES 125 MG

1.2 Dosage Strength

Each hard gelatin capsule contains:

Palbociclib ..... 125 mg

Excipients ..... Q.S.

Approved colors used in capsule shell..

1.3 Dosage Form

A Maroon/Maroon colored hard gelatin capsule size '0' contains yellow colored powder. (Hard Gelatin Capsule)

2. COMPOSITION

Qualitative Declaration

Each hard gelatin capsule contains:

Palbociclib ..... 125 mg

Excipients ..... Q.S.

This product contains lactose.

For the full list of excipients, see section 6.1.

Approved colors used in capsule shell

3. PHARMACEUTICAL FORM

PALBOCICLIB CAPSULES 125 MG, available as A Maroon/Maroon colored hard gelatin capsule size '0' contains yellow

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PALBOCICLIB CAPSULES 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 endocrin-ebased therapy in postmenopausal women or in men; or fulvestrant in patients with disease progression following endocrine therapy

4.2 Posology and method of administration

The recommended dose of PALBOCICLIB CAPSULES 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 CAPSULES should be taken with food [see Clinical Pharmacology (12.3)]. Administer the

recommended dose of an aromatase inhibitor when given with PALBOCICLIB CAPSULES . Please refer to the Full Prescribing Information for the aromatase inhibitor being used. When given with PALBOCICLIB CAPSULES , the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant.

Patients should be encouraged to take their dose of PALBOCICLIB CAPSULES at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. PALBOCICLIB CAPSULES capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination PALBOCICLIB CAPSULES plus fulvestrant therapy should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards.

For men treated with combination PALBOCICLIB CAPSULES plus aromatase inhibitor therapy, consider treatment with an LHRH agonist according to current clinical practice standards.

Dose Modification

The recommended dose modifications for adverse reactions are listed in Tables 1, 2, and 3.

Table 1. Recommended Dose Modification 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.

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Table 2. Dose Modification and Management – Hematologic Toxicitiesa

Monitor complete blood counts prior to the start of PALBOCICLIB CAPSULES 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, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

CTCAE grade	**Dose modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3[a]	Day 1 of cycle: Withhold Palbociclib Capsules, until recovery to Grade ≤ 2, and repea 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 Capsules 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 neutropenia[b] with fever ≥38.5 °C and/or infection	At any time: Withhold Palbociclib Capsules until recovery to Grade ≤2 Resume at the next lower dose.
Grade 4[a]	At any time: Withhold Palbociclib Capsules 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=lower limit 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/mm^3; Grade 2: ANC 1,000 - < 1,500/mm^3; Grade 3: ANC 500 - < 1,000/mm^3; Grade 4: ANC < 500/mm^3.

Table 3. Dose Modification and Management – Non-Hematologic Toxicities

CTCAE grade	**Dose modifications**
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.

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events.

Refer to the Full Prescribing Information for coadministered endocrine therapy dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

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 coadministered a strong CYP3A inhibitor, reduce the PALBOCICLIB CAPSULES dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the PALBOCICLIB CAPSULES dose (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Dose Modifications for Hepatic Impairment

No dose adjustment 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 CAPSULES is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

4.3 Contraindications

None.

4.4 Special warning and precautions

for use 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 CAPSULES plus letrozole in Study 1 and 66% of patients receiving PALBOCICLIB CAPSULES 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 dyas

Monitor complete blood counts prior to starting Palbociclib Capsules 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 Capsules 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 **Embryo-Fetal Toxicity**

Based on findings from animal studies and its mechanism of action, Palbociclib Capsules 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 Capsules and for at least 3 weeks after the last dose.

4.5 Interaction with other medicinal products and other forms of interaction

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, and voriconazole). Avoid grapefruit or grapefruit juice during Palbociclib Capsules treatment. If coadministration of Palbociclib Capsules with a strong CYP3A inhibitor cannot be avoided, reduce the dose of Palbociclib Capsules.

7.2 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 Wor.t) **Drugs That May Have Their Plasma Concentrations Altered by Palbociclib** Coadministration of midazolam with multiple doses of

Palbociclib Capsules increased the midazolam plasma exposure by 61%, in healthy subjects, 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 Capsules may increase its exposure

4.6 Pregnancy and lactation

Pregnancy

Risk

Summary

Based on findings from animal studies and its mechanism of action, PALBOCICLIB CAPSULES can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. 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 [see Data]. 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.

Data 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.

Lactation

Risk Summary

There is no information regarding the presence of palbociclib in human milk, its effects on milk production, or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from PALBOCICLIB CAPSULES , advise a lactating woman not to breastfeed during treatment with PALBOCICLIB CAPSULES and for 3 weeks after the last dose.

Females and Males of Reproductive Potential Pregnancy Testing

Based on animal studies, Palbociclib Capsules 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 Capsules.

Contraception Females

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

Infertili

ty

Males

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

Pediatric Use

The safety and efficacy of PALBOCICLIB CAPSULES 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 27week 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 Capsules 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 Capsules in Study 2, 86 patients (25%) were ≥65 years of ge and 27 patients (8%) were ≥75 years of age. No overall differences in safety or effectivenes of Palbociclib Capsules 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 CAPSULES is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days [see Dosage and Administration (2.2)]. 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 machine

None.

4.8 Undesirable effects:

Summary of the safety profile

The overall safety profile of PALBOCICLIB CAPSULES is based on pooled data from 872 patients who received palbociclib in combination with endocrine therapy (N=527 in combination with letrozole and N=345 in combination with fulvestrant) in randomised clinical studies in HR-positive, HER2-negative advanced or metastatic breast cancer.

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 CAPSULES in randomised clinical studies regardless of the combination.

Permanent discontinuation due to an adverse reaction occurred in 5.2% of patients receiving PALBOCICLIB CAPSULES in randomised clinical studies

regardless of the combination.

Tabulated list of adverse reactions

Table 4 reports the adverse reactions from the pooled dataset of 3 randomised studies. The median duration of palbociclib treatment across the pooled dataset at the time of the final OS analysis was 14.8 months.

Table 5 reports the laboratory abnormalities observed in pooled datasets from 3 randomised studies.

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.

Table 4. Adverse reactions based on pooled dataset from 3 randomised studies (N=872)

System Organ Class **Frequency** **Preferred term[a] (PT)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Infections and infestations *Very common*			
Infections[b]	516 (59.2)	49 (5.6)	8 (0.9)
Blood and lymphatic system disorders *Very common*			
Neutropenia[c]	716 (82.1)	500 (57.3)	97 (11.1)
Leukopenia[d]	424 (48.6)	254 (29.1)	7 (0.8)
Anaemia[e]	258 (29.6)	45 (5.2)	2 (0.2)
Thrombocytopenia[f]	194 (22.2)	16 (1.8)	4 (0.5)
Common			
Febrile neutropenia	12 (1.4)	10 (1.1)	2 (0.2)
Metabolism and nutrition disorders *Very common*			
Decreased appetite	152 (17.4)	8 (0.9)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	79 (9.1)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	48 (5.5)	1 (0.1)	0 (0.0)

Lacrimation increased	59 (6.8)	0 (0.0)	0 (0.0)
Dry eye	36 (4.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders *Common*			
Epistaxis ILD/pneumonitis[*,i]	77 (8.8) 12 (1.4)	0 (0.0) 1 (0.1)	0 (0.0) 0 (0.0)
Gastrointestinal disorders *Very common*			
Stomatitis[g]	264 (30.3)	8 (0.9)	0 (0.0)
Nausea	314 (36.0)	5 (0.6)	0 (0.0)
Diarrhoea	238 (27.3)	9 (1.0)	0 (0.0)
Vomiting	165 (18.9)	6 (0.7)	0 (0.0)

Skin and subcutaneous tissue disorders *Very common*			
Rash[h]	158 (18.1)	7 (0.8)	0 (0.0)
Alopecia	234 (26.8)	N/A	N/A
Dry skin *Uncommon* Cutaneous lupus erythematosus*	93 (10.7) 1 (0.1)	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)
General disorders and administration site conditions *Very common*			
Fatigue	362 (41.5)	23 (2.6)	2 (0.2)
Asthenia	118 (13.5)	14 (1.6)	1 (0.1)
Pyrexia	115 (13.2)	1 (0.1)	0 (0.0)
Investigations *Very common*			
ALT increased	92 (10.6)	18 (2.1)	1 (0.1)
AST Increased	99 (11.4)	25 (2.9)	0 (0.0)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease; N/n=number of patients; N/A=not applicable.
* Adverse drug reaction identified post-marketing.
[a] PTs are listed according to MedDRA 17.1.
[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.
[c] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.
[d] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.
[e] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.
[f] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.
[g] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
[h] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.
[i] ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial Lung Disease (narrow).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

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

measures.

5- Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EF01.

Mechanism of action

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 (Rb) protein 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 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.

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.

Pharmacodynamics

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.

5.2 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 CAPSULES 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

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 inter subject variability of palbociclib exposure, which supports administration of Palbociclib Capsules with food. Compared to Palbociclib Capsules 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 Capsules 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%.

MetabolismIn 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.

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 Capsules have not been evaluated in patients <18 years of age.

Hepatic Impairment

relative to subjects with normal hepatic function. Palbociclib unbound Cmax 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, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib, further supporting the findings from the dedicated hepatic impairment study.

Renal Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that palbociclib 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 (Cr Cl <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. In addition, based on a population pharmacokinetic analysis that included 183 patients where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

5.3 Preclinical safety data

The primary target organ findings following single and/or repeat dosing included haematolymphopoietic and male reproductive organ effects in rats and dogs, and effects on bone and actively growing incisors in rats only. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. Partial to full reversal of effects on the

hematolymphopoietic, male reproductive systems, and incisor teeth were established, whereas the bone effect was not reversed following a 12-week nondosing period. 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 C_{max}.

Carcinogenicity

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.

6- Pharmaceutical Particulars:

6.1 List of Excipients

Microcrystalline Cellulose

(plain) Lactose

Monohydrate

Sodium starch Glycolate

Colloidal silicon Dioxide

(heavy) Magnesium

Stearate

E.H.G. Capsules Size '0' Maroon/Maroon

6.2 Incompatibilities: Not applicable.

6.3 Shelf life: 36 months from the date of manufacture.

6.4 Special precautions for storage: Store below 30 degrees & dry place. Protect from light.

6.5 Nature and contents of container

21 Capsule packed in a bottle. Such Bottles packed in unit printed 300 GSM, cyber excel board aqua varnish carton, along with its package insert. Such cartons packed in export worthy corrugated box.

7. Marketing Authorization Holder: Globela Pharma Pvt. Ltd.

H2026/CTD11012/23863

8. Date of first authorization:

18/03/2026