**PROFESSIONAL INFORMATION FOR**

**PALBOCICLIB CIPLA CAPSULES**

**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

PALBOCICLIB 75 mg CIPLA (capsules)

PALBOCICLIB 100 mg CIPLA (capsules)

PALBOCICLIB 125 mg CIPLA (capsules)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**PALBOCICLIB 75 mg CIPLA capsules:**

Each capsule contains 75 mg of palbociclib.

Contains sugar: (Lactose monohydrate 55,800 mg)

**PALBOCICLIB 100 mg CIPLA capsules:**

Each capsule contains 100 mg of palbociclib.

Contains sugar: (Lactose monohydrate 74,400 mg)

**PALBOCICLIB 125 mg CIPLA capsules:**

Each capsule contains 125 mg of palbociclib.

Contains sugar: (Lactose monohydrate (93,000 mg)

For the full list of excipients, see **section 6.1.**

## 3. PHARMACEUTICAL FORM

Capsules

**PALBOCICLIB 75 mg CIPLA:** Yellow colour blend, filled in size '2' opaque, hard gelatin capsules, with light orange cap and body, printed with black ink "Cipla" on the cap and "75 mg" on the body.

**PALBOCICLIB 100 mg CIPLA:** Yellow colour blend, filled in size '1' opaque, hard gelatin capsules, with caramel cap and light orange body, printed with black ink "Cipla" on the cap and "100 mg" on the body.

**PALBOCICLIB 125 mg CIPLA:** Yellow colour blend, filled in size '0' opaque, hard gelatin capsules, with caramel cap and body, printed with black ink "Cipla" on the cap and "125 mg" on the body.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

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

- with letrozole as initial endocrine-based therapy in postmenopausal women
- with fulvestrant in women with disease progression who have received prior endocrine therapy.

### 4.2. Posology and method of administration

Treatment with PALBOCICLIB CIPLA should be conducted by a medical practitioner experienced in the use of anticancer therapies.

**Posology**

The recommended starting dose of PALBOCICLIB CIPLA is a 125 mg capsule taken orally once daily with food for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days.

When co-administered with PALBOCICLIB CIPLA, the recommended dose of letrozole is 2,5 mg taken orally once daily continuously throughout the 28-day cycle. Please refer to the full prescribing information of letrozole.

When co-administered with PALBOCICLIB CIPLA the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the Professional Information of fulvestrant.

Patients should be encouraged to take their dose at approximately the same time each day. Continue the treatment as long as the patient is deriving clinical benefit from therapy.

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 CIPLA capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Prior to the start of, and throughout treatment with the combination PALBOCICLIB CIPLA plus fulvestrant, pre/perimenopausal women should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

*Dose modifications*

Dose modification of PALBOCICLIB CIPLA is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dose interruptions/ cycle delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2, and 3 (see **sections 4.4** and **4.8**).

**Table 1. PALBOCICLIB CIPLA 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.

**Table 2. PALBOCICLIB CIPLA dose modification and management –haematologic toxicities**

Monitor complete blood counts prior to the start of PALBOCICLIB CIPLA 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:<br>Withhold PALBOCICLIB CIPLA, 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.<br><br>Day 15 of first 2 cycles:<br>If Grade 3 on Day 15, continue PALBOCICLIB CIPLA at the *current* dose to complete cycle and repeat complete blood count on Day 22.<br><br>If Grade 4 on Day 22, see Grade 4 dose modification guidelines below.<br><br>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]<br>(<1,000 to 500/mm$^3$) + | At any time:<br>Withhold PALBOCICLIB CIPLA until recovery to Grade ≤ 2 |

| | |
|---|---|
| Fever ≥ 38.5 °C and/or infection | Resume at next lower dose. |
| Grade 4[a] | At any time:<br>Withhold PALBOCICLIB CIPLA until recovery to Grade ≤ 2.<br>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. PALBOCICLIB CIPLA dose modification and management –** non-haematologic **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:<br>• Grade ≤ 1;<br>• Grade ≤ 2 (if not considered a safety risk for the patient)<br>Resume at the next lower dose. |

Grading according to CTCAE 4.0.

CTCAE = Common Terminology Criteria for Adverse Events.

Permanently discontinue PALBOCICLIB CIPLA in patients with severe interstitial lung disease (ILD)/pneumonitis (see **section 4.4**).

No dose modifications are required on the basis of patient's age, sex or body weight (see **section 5.2**).

**Special populations**

*Elderly population*

No dose adjustment is necessary in patients ≥ 65 years of age (see **section 5.2**).

*Hepatic impairment*

No dose adjustment of PALBOCICLIB CIPLA 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 CIPLA is 75 mg once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days (see **sections 4.4** and **5.2**).

*Renal impairment*

No dose adjustment 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 dosing recommendation in this patient population.

**Paediatric population**

The safety and efficacy of PALBOCICLIB CIPLA in children and adolescents < 18 years of age have not been established.

## 4.3. Contraindications

- Hypersensitivity to the active substance, palbociclib or to any of the excipients listed in **section 6.1**.
- Use of preparations containing St. John's Wort (see **section 4.5**).

## 4.4. Special warnings and precautions for use

Neutropenia

Decreased neutrophil counts have been observed in clinical studies with PALBOCICLIB CIPLA. In patients receiving PALBOCICLIB CIPLA in combination with letrozole (Study 1 and 2) or fulvestrant (Study 3), Grade 3 and Grade 4 decreased neutrophil counts were reported in 56,1 % and 10,6 % of patients, respectively.

The median time to first episode of any grade neutropenia was 15 days (12 - 700 days) and the median duration of Grade ≥ 3 neutropenia was 7 days across 3 randomised clinical studies.

Monitor complete blood count prior to starting PALBOCICLIB CIPLA 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.

Treatment interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia (see **section 4.2**).

Pre/perimenopausal women

Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered PALBOCICLIB CIPLA 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 (see **section 5.1**).

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 (see **sections 4.2** and **4.8**).

Interstitial lung disease/pneumonitis (ILD)

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with cyclin-dependent kinase (CDK 4/6) inhibitors, including PALBOCICLIB CIPLA when taken in combination with endocrine therapy.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.4 % of PALBOCICLIB CIPLA-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 (see **section 4.8**).

Monitor patients 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, interrupt PALBOCICLIB CIPLA immediately and evaluate the patient. Permanently discontinue PALBOCICLIB CIPLA in patients with severe ILD or pneumonitis (see **section 4.2**).

Infections

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

Infections of any grade have been reported at a higher rate in patients treated with PALBOCICLIB CIPLA in randomised clinical studies compared to patients treated in the respective comparator arm. Grade 3 and Grade 4 infections occurred respectively in 4,4 % and 0,7 % of patients treated with PALBOCICLIB CIPLA in any combination (see **section 4.8**).

Patients should be monitored for signs and symptoms of infection and treated as medically appropriate (see **section 4.2**).

Medical practitioners should inform patients to promptly report any episodes of fever.

Hepatic impairment

Administer PALBOCICLIB CIPLA with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity (see **sections 4.2** and **5.2**).

Renal impairment

Administer PALBOCICLIB CIPLA with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity (see **sections 4.2** and **5.2**).

Concomitant treatment with inhibitors or inducers of CYP3A4

Strong inhibitors of CYP3A4 may lead to increased toxicity (see **section 4.5**). Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Co-administration should only be considered after careful evaluation of the potential benefits and risks. If co-administration with a strong CYP3A inhibitor is unavoidable, reduce the PALBOCICLIB CIPLA dose to 75 mg once daily. When the strong inhibitor is discontinued, increase the PALBOCICLIB CIPLA dose (after 3 – 5 half – lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see **section 4.5**).

Concomitant use of palbociclib with strong CYP3A4 inducers should be avoided since coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. No dose adjustments are required for co-administration of palbociclib with moderate CYP3A inducers (see **section 4.5**).

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 CIPLA (see **section 4.6**).

Lactose Monohydrate

PALBOCICLIB CIPLA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption should not

take this medicine. PALBOCICLIB CIPLA may have an effect on the glycaemic control of patients with diabetes mellitus.

Sodium

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

## 4.5. Interaction with other medicines and other forms of 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 medicines 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 ($AUC_{inf}$) and the peak concentration ($C_{max}$) 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: amprenavir, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided (see **sections 4.2** and **4.4**).

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

*Medicines that may decrease PALBOCICLIB CIPLA plasma concentrations.*

*Effect of CYP3A inducers*

Coadministration of multiple 600 mg doses of rifampicin with a single 125 mg palbociclib dose decreased palbociclib $AUC_{inf}$ and $C_{max}$ by 85 % and 70 %, respectively, relative to a single 125 mg palbociclib dose given alone.

The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin, rifapentine, and St. John's Wort should be avoided (see **sections 4.3** and **4.4**).

Coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg PALBOCICLIB CIPLA dose decreased palbociclib $AUC_{inf}$ and $C_{max}$ by 32 % and 11 %, respectively, relative to a single 125 mg PALBOCICLIB CIPLA dose given alone.

No dose adjustments are required for moderate CYP3A inducers (see **section 4.4**).

Effect of acid reducing medicines

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 CIPLA decreased palbociclib $C_{max}$ by 41 % but had limited impact on $AUC_{inf}$ (13 % decrease) compared with a single dose of 125 mg PALBOCICLIB CIPLA administered alone.

Under fasting conditions, the coadministration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg PALBOCICLIB CIPLA decreased palbociclib $AUC_{inf}$ and $C_{max}$ by 62 % and 80 %, respectively. Therefore, PALBOCICLIB CIPLA should be taken with food, preferably a meal (see **sections 4.2** and **5.2**).

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 CIPLA is taken with food.

Effects of palbociclib on the pharmacokinetics of other medicines

Palbociclib is a weak, time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state in humans. Coadministration of multiple doses of palbociclib with midazolam increased the midazolam AUCinf and $C_{max}$ values by 61 % and 37 %, respectively, as compared with administration of midazolam alone.

*In vitro*, palcociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not

an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

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 co-administered with PALBOCICLIB CIPLA as PALBOCICLIB CIPLA 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 medicines were co-administered.

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 co-administered with multiple doses of tamoxifen and when palbociclib was given alone.

Drug-drug interaction between palbociclib and fulvestrant

Data available in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the two medicines were co-administered.

Drug-drug interaction between palbociclib and oral contraceptives

There is no date available on DDI studies of palbociclib with oral contraceptives (see **section 4.6**).

*In vitro* studies with transporters

*In vitro* evaluations indicate that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp, systemically), breast cancer resistance protein (BCRP,

systemically), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, and bile salt export pump (BSEP) at clinically relevant concentrations. *In vitro*, palbociclib has the potential to inhibit OCT1 at clinically relevant concentrations, as well as the potential to inhibit P-gp or BCRP in the gastrointestinal tract at the proposed clinical dose. Based on *in vitro* data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses.

## 4.6. Fertility, pregnancy and lactation

**Women of childbearing potential/Contraception**

Females of childbearing potential who are receiving this medicine, 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 adequate and well-controlled studies using PALBOCICLIB CIPLA in pregnant women. Based on findings in animals and mechanism of action, PALBOCICLIB CIPLA can cause foetal harm when administered to a pregnant woman. In animal studies, PALBOCICLIB CIPLA was teratogenic and foetotoxic at maternally toxic doses.

**Breastfeeding**

It is unknown whether palbociclib is excreted in human milk as 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. Patients receiving PALBOCICLIB CIPLA should not breast feed.

**Fertility**

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 CIPLA. Thus, men may consider sperm preservation prior to beginning therapy with PALBOCICLIB CIPLA.

### 4.7. Effects on ability to drive and use machines

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

### 4.8. Undesirable effects

**Infections and infestations**

| | |
|---|---|
| Frequent: | Infections[b] |

**Blood and lymphatic system disorders**

| | |
|---|---|
| Frequent: | Neutropenia[c] (neutropenia, decreased neutrophil count), Leukopeniad (leukopenia, decreased white blood cell count), Anaemia[e] (anaemia, decreased haemoglobin, decreased haematocrit), Thrombocytopenia[f] (thrombocytopenia, decreased platelet count), Febrile neutropenia |

**Metabolism and nutrition disorders**

| | |
|---|---|
| Frequent: | Decreased appetite |

**Nervous system disorders**

| | |
|---|---|
| Frequent: | Dysgeusia |

**Eye disorders**

| | |
|---|---|
| Frequent: | Vision blurred, Lacrimation increased, Dry eye |

**Respiratory, thoracic and mediastinal disorders**

| | |
|---|---|
| Frequent: | Epistaxis |

**Gastrointestinal disorders**

| | |
|---|---|
| Frequent: | Stomatitis[g] (aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis), Nausea, Diarrhoea, Vomiting |

**Skin and subcutaneous tissue disorders**

| | |
|---|---|
| Frequent: | Rash[h] (rash, maculo-papular rash, pruritic rash, erythematous rash, papular rash, dermatitis, acneiform dermatitis, toxic skin eruption), Alopecia, Dry skin |

**General disorders and administration site conditions**

| | |
|---|---|
| Frequent: | Fatigue, Asthenia, Pyrexia |

**Investigations**

| | |
|---|---|
| Frequent: | Increased alanine aminotransferase, increased aspartate aminotransferase |

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ILD=interstitial lung disease; N/n=number of patients; N/A=not applicable.

[a] Preferred Terms (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.

Post-marketing adverse events

| | |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | ILD/pneumonitis* |
| **Skin and subcutaneous tissue disorders** | Cutaneous lupus erythematosus |

* ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial Lung Disease (narrow)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

### 4.9. Overdose

There is no antidote for PALBOCICLIB CIPLA.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic medicines, protein kinase inhibitors, ATC code: L01XE33.

Palbociclib is taken orally and is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation.

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 oestrogen receptor ER-positive breast cancers. Mechanistic analyses revealed that the combination of palbociclib with anti-oestrogen medicines enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signalling and growth arrest. The enhanced growth arrest of the ER-positive breast cancer cell lines treated with palbociclib and anti-oestrogen medicines is accompanied by increased cell senescence resulting in a sustained cell cycle arrest following drug removal and increased cell size associated with a senescent phenotype. *In vivo* studies using a patient-derived ER-positive breast cancer xenograft model (HBCx-34) demonstrated that the combination of palbociclib and letrozole further enhanced inhibition of Rb phosphorylation, downstream signalling and dose-dependent tumour growth. This supports the contribution of senescence-associated growth arrest as a mechanism associated with the anti-tumour efficacy of combined palbociclib/ER antagonist in ER-positive breast cancer models.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched electrocardiogram (ECG) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with advanced breast cancer. Palbociclib did not prolong the QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

**Clinical efficacy and safety**

*Randomised study of palbociclib in combination with letrozole (PALOMA-1).*

The primary endpoint of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1,0.

The median PFS (mPFS) for patients in the palbociclib plus letrozole arm was 20,2 months (95 % confidence interval [CI]: 13,8; 27,5) and 10,2 months (95 % CI: 5,7; 12,6) for patients in the letrozole-alone arm. The observed hazard ratio (HR) was 0,488 (95 % CI: 0,319; 0,748) in favour of albociclib plus letrozole, with a stratified log-rank test 1-sided p-value of 0,0004.

*Randomised Study of palbociclib in combination with letrozole (PALOMA-2)*

The primary endpoint of the study was PFS evaluated according to RECIST version 1,1 as assessed by investigator. Secondary efficacy endpoints included objective response (OR), duration of response (DOR), clinical benefit response (CBR), overall survival (OS), safety, EQ-5D scores and health-related quality of life (QoL) assessed using the FACT-B questionnaire.

The study met its primary objective of improving PFS. The estimated HR was 0,576 (95 % CI: 0,463; 0,718) in favour of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of < 0,000001. The mPFS for patients in the palbociclib plus letrozole arm was 24,8 months (95 % CI: 22,1, Not estimable [NE]) and 14,5 months (95 % CI: 12,9; 17,1) for patients in the placebo plus letrozole arm. The treatment effect of the combination on PFS was also supported by an independent review of radiographs with an estimated HR of 0,653 (95 % CI: 0,505; 0,844).

*Randomised, Phase 3 study of palbociclib in combination with fulvestrant*

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST version 1,1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, DOR, CBR, OS, safety, change in QoL, and TTD. Patient-reported outcomes including Global QoL and pain were measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Breast Cancer Module (BR23) questionnaire.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82 % of the planned PFS events at final analysis; the results crossed the prespecified Haybittle-Peto efficacy boundary (α = 0,00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect.

The estimated HR from the stratified analysis was 0,422 (95 % CI: 0,318; 0,560; 1-sided p < 0,000001) in favour of palbociclib plus fulvestrant.

The mPFS was 9,2 months (95 % CI: 7,5; NE) in the palbociclib plus fulvestrant arm and 3,8 months (95 % CI: 3,5; 5,5) in the placebo plus fulvestrant arm.

## 5.2. Pharmacokinetic properties

The pharmacokinetics of palbociclib were characterised in patients with solid tumours including advanced breast cancer and in healthy volunteers.

Absorption

The mean time to $C_{max}$ ($T_{max}$) of palbociclib is generally observed between 4 to 8 hours 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 area under the curve (AUC) and $C_{max}$ increase proportionally with dose in general. Steady state may be achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulates with a median accumulation ratio of 2,4 (range 1,5 – 4,2).

Food effect

Palbociclib absorption and exposure are very low in approximately 13 % of the population under fasted condition. Food intake may increase the palbociclib exposure in this small subset of the population but may not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Compared to palbociclib given under overnight fasted conditions, the $AUC_{inf}$ and $C_{max}$ of palbociclib increased by 21 % and 38 % when given with high-fat food, by 12 % and 27 % when given with low-fat food, and by 13 % and 24 % when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake may significantly reduce the intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib should be taken with food (see **section 4.2**).

Gastric pH elevating medication effect

In a healthy subject study, co-administration of a single 125 mg dose of palbociclib with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib $C_{max}$ by 41 % but had limited impact on $AUC_{inf}$ (13 % decrease), when compared to a single 125 mg dose of palbociclib administered alone.

Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing medicines on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure. In another healthy subject study, co-administration of a single 125 mg dose of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib $AUC_{0\text{-}inf}$ and $C_{max}$ by 62 % and 80 %, respectively, when compared with a single dose of palbociclib administered alone.

Distribution

Binding of palbociclib to human plasma proteins *in vitro* was ~85 %, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The mean fraction unbound ($f_u$) of palbociclib in human plasma *in vivo* increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib $f_u$ in human plasma *in vivo* with worsening renal function. *In vitro*, the uptake of palbociclib into human hepatocytes occurred mainly via passive diffusion. Palbociclib is not a substrate of OATP1B1 or OATP1B3.

The geometric mean apparent volume of distribution (Vz/F) was 2583 (26%) L.

Biotransformation

*In vitro* and *in vivo* studies indicate that palbociclib undergoes extensive hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [$^{14}$C] palbociclib to humans, the major primary metabolic pathways for palbociclib involved oxidation and sulphonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma.

The majority of the material was excreted as metabolites. In faeces, the sulphamic acid conjugate of palbociclib was the major drug-related component, accounting for 25,8 % of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulphotransferase (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 L/h, and the mean plasma elimination half-life was 28,8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [$^{14}$C] palbociclib, a median of 92 % of the total administered radioactive dose was recovered in 15 days; faeces (74 % of dose) was the major route of excretion, with 17 % of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2 % and 7 % of the administered dose, respectively.

*In vitro*, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

*In vitro* evaluations indicate that palbociclib has low potential to inhibit the activities of organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, and bile salt export pump (BSEP) at clinically relevant concentrations.

Special 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.

*Elderly population*

No differences in safety or effectiveness of palbociclib in patients ≥ 65 years of age and younger patients.

*Hepatic impairment*

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound $AUC_{in}f$) 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 $C_{max}$) 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 trial 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 ($C_{max}$) 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.

*Ethnicity*

In a pharmacokinetic study in healthy volunteers, palbociclib $AUC_{inf}$ and $C_{max}$ 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.

*Paediatric population*

There is no data available on the pharmacokinetics of palbociclib in patients < 18 years of age.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

The other ingredients are:

Capsule content

- Lactose Monohydrate (200 mesh)
- Microcrystalline Cellulose (Avicel pH 102)
- Sodium Starch Glycolate (Type A)
- Magnesium stearate (Vegetable Grade)
- Colloidal silicon dioxide (Aerosil)

Capsule shell

- Iron oxide red
- Iron oxide yellow
- Titanium dioxide
- Gelatin
- Water

Printing ink

- Shellac
- Dehydrated Alcohol
- Isopropyl Alcohol
- Butyl Alcohol
- Propylene Glycol
- Strong Ammonia Solution
- Black Iron Oxide
- Potassium Hydroxide

### 6.2. Incompatibilities

Not applicable

### 6.3. Shelf life

24 months

### 6.4. Special precautions for storage

This medicine does not require any special storage conditions.

### 6.5. Nature and contents of container

PALBOCICLIB CIPLA 75 mg, 100 mg and 125 mg capsules are packed in HDPE container of 21’s with 33MM 400 Argus LOC Blue Child Resistant cap.

### 6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

**CIPLA MEDPRO (PTY) LTD**

Parc du Cap

Building 9

Mispel Street

Bellville

7530

RSA

Customer Care: 080 222 6662

## 8. REGISTRATION NUMBER(S)

PALBOCICLIB 75 mg CIPLA: 56/26/0161

PALBOCICLIB 100 mg CIPLA: 56/26/0162

PALBOCICLIB 125 mg CIPLA: 56/26/0163

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 February 2023

## 10. DATE OF REVISION OF THE TEXT

Not applicable.