APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PALVORED 75/ 100/ 125, Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PALVORED 75

Each hard gelatin capsule contains 75,00 mg palbociclib.

Contains sugar (lactose monohydrate 55,78 mg per capsule).

PALVORED 100

Each hard gelatin capsule contains 100,00 mg palbociclib.

Contains sugar (lactose monohydrate 74,37 mg per capsule).

PALVORED 125

Each hard gelatin capsule contains 125,00 mg palbociclib.

Contains sugar (lactose monohydrate 92,96 mg per capsule).

For the full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

Capsules.

PALVORED 75

Pale yellow to yellow granular powder filled in hard gelatin capsules, with light yellow opaque cap and light yellow opaque body, printed with black ink "DRL" on cap and "PLB 75" on body.

PALVORED 100

Pale yellow to yellow granular powder filled in hard gelatin capsules, with gray opaque cap and light yellow opaque body, printed with black ink "DRL" on cap and "PLB 100" on body.

PALVORED 125

Pale yellow to yellow granular powder filled in hard gelatin capsules, with light gray opaque cap and light yellow opaque body, printed with black ink "DRL" on cap and "PLB 125" on body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PALVORED 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 PALVORED should be conducted by a medical practitioner experienced in the use of anticancer therapies.

Posology:

The recommended starting dose of PALVORED 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 PALVORED, 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 PALVORED, the recommended dose of fulvestrant is 500 mg administered intramuscularly 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 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. PALVORED 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 PALVORED 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 PALVORED is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dosing 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. PALVORED Recommended dose modifications for adverse events

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. PALVORED Dose modification and management – haematologic toxicities[a]

Monitor complete blood counts prior to the start of PALVORED 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 PALVORED, 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 PALVORED 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 the subsequent cycles.
Grade 3 ANC[b] (< 1 000 to 500/mm^3) + fever ≥ 38,5 ºC and/or infection	At any time: Withhold PALVORED until recovery to Grade ≤ 2. Resume at the *next lower dose.*
Grade 4[a]	At any time: Withhold PALVORED until recovery to Grade ≤ 2. Resume at the *next lower dose.*

Grading according to CTCAE 4,0 (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).

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal.

[a] Table applies to all haematologic 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. PALVORED Dose modification and management – non-haematologic toxicities

CTCAE Grade	**Dose modifications**
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-haematologic 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.

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

Permanently discontinue PALVORED in patients with severe interstitial lung disease (ILD) or pneumonitis (see section 4.4).

Special populations

Elderly population

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

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 PALVORED 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 section 4.1 and section 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 PALVORED in children and adolescents ≤ 18 years of age have not been established.

Method of administration:

For oral administration.

The capsule should be swallowed whole with food.

4.3 Contraindications

Hypersensitivity to palbociclib or any of the excipients of PALVORED (listed in section 6.1).

Use of preparations containing St. John's Wort.

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 PALVORED 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).

Neutropenia

Decreased neutrophil counts have been observed in clinical studies with palbociclib. In patients

receiving palbociclib in combination with letrozole or fulvestrant, 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.

Monitor complete blood count prior to starting PALVORED 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).

Interstitial lung disease/pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with PALVORED when taken in combination with endocrine therapy.

Across studies, 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 reported (see section 4.8).

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, PALVORED should be immediately interrupted and the patient should be evaluated. PALVORED should be permanently discontinued in patients with severe ILD or pneumonitis (see section 4.2).

Infections

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

Infections have been reported at a higher rate in patients treated with palbociclib plus letrozole or fulvestrant 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 (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

PALVORED should be administered 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

PALVORED should be administered 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. 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 PALVORED dose to 75 mg once daily. When the strong inhibitor is discontinued, the dose of PALVORED should be increased (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).

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 (see section 4.5).

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with palbociclib (see section 4.8). Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism, and treated as medically

appropriate.

Excipients with known effect:

Lactose

This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

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: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, amprenavir, atazanavir, boceprevir, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, mibefradil, miconazole 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.

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, primidone, rifabutin, phenytoin, rifampicin, 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 dose decreased palbociclib AUC_{inf} and C_{max} by 32 % and 11 %, respectively, relative to a single 125 mg palbociclib 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 decreased palbociclib C_{max} by 41 %, but had limited impact on AUC_{inf} (13 % decrease) compared with a single dose of 125 mg PALVORED administered alone.

Under fasting conditions, the coadministration of multiple doses of the PPI rabeprazole with a single dose of 125 mg palbociclib decreased palbociclib AUC_{inf} and C_{max} by 62 % and 80 %, respectively. Therefore, PALVORED 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 PALVORED 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. Coadministration of multiple doses of palbociclib with midazolam increased the midazolam AUC_{inf} and C_{max} 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 PALVORED as PALVORED may increase their exposure.

Drug-drug interaction between palbociclib and letrozole

Data from a study in patients with breast cancer showed that there was no medicine interaction between palbociclib and letrozole when the 2 medicines were coadministered.

Effect of tamoxifen on palbociclib exposure

Data from a 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 study in patients with breast cancer showed that there was no clinically relevant medicine interaction between palbociclib and fulvestrant when the two medicines were coadministered.

Goserelin

Data from a clinical study in patients with breast cancer showed that there were no clinically relevant interactions between palbociclib and goserelin when the two medicines were co-administered.

Drug-drug interaction between palbociclib and oral contraceptives

Studies of palbociclib with oral contraceptives have not been conducted (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 in males and females

Females of childbearing potential who are receiving PALVORED, 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 (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of palbociclib in pregnant women.

Based on findings in animals and the mechanism of action, palbociclib can cause foetal harm when administered to a pregnant woman. In animal studies, palbociclib was teratogenic and foetotoxic at maternally toxic doses.

PALVORED is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

No studies have been conducted in humans 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 PALVORED should not breast-feed.

Fertility

There were no effects on oestrous cycle (female rats) or mating and fertility in rats (male or female) in reproductive studies. However, no data have been obtained on fertility in humans. Based on male reproductive organ findings in nonclinical studies, male fertility may be compromised by treatment with palbociclib. Thus, men may consider sperm preservation prior to beginning therapy with PALVORED.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent adverse drug reactions of any grade reported in patients receiving palbociclib were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, alopecia, and diarrhoea.

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: with in each frequency grouping, and listed in the table below.

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Infections[a]		
Blood and lymphatic system disorders	Neutropenia[b] Leukopenia[c] Anaemia[d] Thrombocytopenia[e] Febrile neutropenia		
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Dysgeusia		
Eye disorders	Vision blurred Lacrimation increased Dry eye		
Vascular disorders			Venous thromboembolism*[i]
Respiratory, Thoracic and Mediastinal Disorders	Epistaxis		ILD/pneumonitis*[h]
Gastrointestinal disorders	Stomatitis[f] Nausea Vomiting Diarrhoea		
Skin and subcutaneous tissue	Rash[g] Alopecia		Palmar-plantar erythrodysaesthesia

disorders	Dry skin		syndrome* Cutaneous lupus erythematosus*
General Disorders and administration site condition	Fatigue Asthenia Pyrexia		
Investigations	ALT=Alanine aminotransferase increased AST = Aspartate aminotransferase increased		

ALT=alanine aminotransferase; AST=aspartate aminotransferase;

ILD=interstitial lung disease

* Adverse drug reaction identified post-marketing.

[a] Infections includes all PTs that are part of the System Organ Class Infections and infestations.

[b] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

[c] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.

[d] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.

[e] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.

[f] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

[g] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

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

[i] Venous thromboembolism includes the following PTs: pulmonary embolism, embolism, deep vein thrombosis, peripheral embolism, thrombosis.

Description of selected adverse reactions

Overall, neutropenia of any grade was reported in 82,1 % patients receiving palbociclib regardless of the combination, with Grade 3 neutropenia being reported in 57,3 % patients, and Grade 4 neutropenia reported in 11,1 % patients.

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

Febrile neutropenia has been reported in 0,9 % of patients receiving palbociclib in combination with fulvestrant and in 1,7 % of patients receiving palbociclib in combination with letrozole. Febrile neutropenia has been reported in about 2 % of patients exposed to palbociclib.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

There is no known antidote for PALVORED. In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and haematological (e.g., neutropenia) toxicity may occur and general supportive care should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacological classification - A.26 Cytostatic agents.

Mechanism of action

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

Pharmacodynamic effects

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 efficacy 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 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).

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 C_{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 was 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 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. 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 significantly reduced the inter subject 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 medicine-derived entity in plasma. The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1,5 % of the administered dose in the excreta.

The majority of the material was excreted as metabolites. In faeces, the sulfamic acid conjugate of palbociclib was the major medicine-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 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) were 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 patients with cancer (male and 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.

Hepatic impairment

Data from a pharmacokinetic study in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound AUC_{inf}) 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 study in subjects with varying degrees of renal function indicate that total

palbociclib exposure (AUC_{inf}) 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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Silicon Dioxide

Lactose Monohydrate

Magnesium Stearate

Microcrystalline Cellulose

Sodium Starch Glycolate

Capsule Shell Ingredients

Gelatin

Iron Oxide Yellow (Ferric oxide Yellow) (Palvored 75/ Palvored 100/ Palvored 125)

Iron Oxide Black (Ferrosoferric Oxide) (Palvored 100/ Palvored 125)

Titanium Dioxide

Water

The printing Ink contains

Black Iron Oxide

Butyl Alcohol

Dehydrated Alcohol

Isopropyl Alcohol

Potassium Hydroxide

Propylene Glycol

Purified Water

Shellac

Strong Ammonium Solution

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep well closed after first opening of the container.

Keep blisters in carton until required for use.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

PACK SIZES 21's:

Bottle pack: PALVORED is packed in multi-layer bottles 60 cc closed with child resistant plastic cap with pulp liners (33 mm), and a silica gel sachet in a pack.

Blister Pack: PALVORED is packed in cold formable foil (width 164 mm), Aluminium foil paper backed peel push plain (width 165 mm) in a pack size of 21 capsules (Each blister contains 7 capsules 3 X 7

= 21 capsules) in a box.

6.6 Special precautions for disposal and other handling

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBER(S)

PALVORED 75: 57/26/0520

PALVORED 100: 57/26/0521

PALVORED 125: 57/26/0522

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 August 2025

10. DATE OF REVISION OF TEXT

Not applicable.