For use in India only

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Palbociclib Tablets 75 mg, 100 mg and 125 mg

Palborest® 75/100/125
पालबोरेस्ट ७५/१००/१२५

To be sold by retail on the prescription of Oncologist only

PRESCRIBING INFORMATION

1. GENERIC NAME
Palbociclib Tablets 75 mg, 100 mg and 125 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Film Coated Tablet Contains
Palbociclib 75 mg
Colours: Titanium Dioxide IP
FerricOxide Red USP-NF
Ferric Oxide Yellow USP-NF

Each Film Coated Tablet Contains
Palbociclib 100 mg
Colours: Titanium Dioxide IP
FerricOxide Red USP-NF
Ferric Oxide Yellow USP-NF

Each Film Coated Tablet Contains
Palbociclib 125 mg
Colours: Titanium Dioxide IP
FerricOxide Red USP-NF
Ferric Oxide Yellow USP-NF

3. DOSAGE FORM AND STRENGTH
Palbociclib is available as a 75 mg, 100 mg and 125 mg tablets

4. CLINICAL PARTICULARS
4.1. Indications
Palbociclib is a kinase inhibitor 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 fulvestrant in women with disease progression following endocrine therapy.

Palbociclib is a kinase inhibitor indicated in combination with Letrozole for the treatment of postmenopausal women with estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine based therapy for their metastatic disease.

Palbociclib is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)- negative advanced or metastatic breast cancer in combination with aromatase inhibitor as initial endocrine-based therapy and with fulvestrant in patients who have received prior therapy for Male patients.

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

Posology
The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. The treatment with Palbociclib should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

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

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

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Dose adjustments
Dose modification of palbociclib is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2, and 3.

Table 1. Palbociclib recommended dose modifications for adverse reactions

Dose level	Dose
Recommended dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*
*If further dose reduction below 75 mg/day is required, discontinue the treatment	

Complete blood count should be monitored prior to the start of Palbociclib therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle and as clinically indicated.

Absolute neutrophil counts (ANC) of ≥ 1,000/mm^3 and platelet counts of ≥ 50,000/mm^3 are recommended to receive palbociclib.

Table 2. Palbociclib dose modification and management – Haematological toxicities

CTCAE grade	Dose modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3[a]	Day 1 of cycle: Withhold Palbociclib, until recovery to Grade ≤ 2, and repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2, start the next cycle at the same dose. Day 15 of first 2 cycles: If Grade 3 on Day 15, continue Palbociclib at the current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (> 1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 ANC[b] (< 1,000 to 500/mm3) + Fever ≥ 38.5 °C and/or infection	At any time: Withhold Palbociclib until recovery to Grade ≤ 2 Resume at next lower dose.
Grade 4[a]	At any time: Withhold Palbociclib until recovery to Grade ≤ 2 Resume at next lower dose.
Grading according to CTCAE 4.0. ANC=absolute neutrophil counts; CTCAE=Common Terminology Criteria for Adverse Events; LLN=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 dose modification and management – Non-haematological 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.	

Permanently discontinue Palbociclib in patients with severe interstitial lung disease (ILD)/pneumonitis.

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

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

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

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

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

Method of administration
Palbociclib is for oral use. The tablets may be taken with or without food. Palbociclib should not be taken with grapefruit or grapefruit juice.
Palbociclib tablets should be swallowed whole (should not be chewed, crushed, or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

4.3. Contraindications
- Hypersensitivity to the active substance or to any of the excipients.
- Use of preparations containing St. John's Wort.

4.4. Special Warnings and Precautions for Use
Neutropenia
Neutropenia was the most frequently reported adverse reaction with an incidence of 83%. A Grade ≥3 decrease in neutrophil counts was reported in 66% of patients receiving Palbociclib plus letrozole and 66% of patients receiving Palbociclib plus fulvestrant. The median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥3 neutropenia was 7 days.

Monitor complete blood counts prior to starting Palbociclib therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in 1.8% of patients exposed to Palbociclib across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever.

Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including Palbociclib when taken in combination with endocrine therapy.

Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt Palbociclib immediately and evaluate the patient. Permanently discontinue Palbociclib in patients with severe ILD or pneumonitis.

5.3 Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, Palbociclib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Palbociclib and for at least 3 weeks after the last dose.

4.5. Drug Interactions
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 treatment. If coadministration of Palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of Palbociclib.

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 Wort).

Drugs That May Have Their Plasma Concentrations Altered by Palbociclib
Coadministration of midazolam with multiple doses of Palbociclib 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 may increase its exposure.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
Based on findings from animal studies and its mechanism of action, Palbociclib can cause fetal harm when administered to a pregnant woman.

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on AUC *(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. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

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

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

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

Lactation
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, advise a lactating woman not to breastfeed during treatment with Palbociclib and for 3 weeks after the last dose.

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

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

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

Infertility
Males
Based on animal studies, Palbociclib may impair fertility in males of reproductive potential.

Pediatric Use
The safety and efficacy of Palbociclib in pediatric patients have not been studied.
Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), kidney (tubule vacuolation, chronic progressive nephropathy) and adipose tissue (atrophy) were identified in a 27 week repeat-dose toxicology study in rats that were immature at the beginning of the studies and were most prevalent in males at oral palbociclib doses ≥30 mg/kg/day (approximately 11 times the adult human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present with lower incidence and severity in a 15 week repeat-dose toxicology study in immature rats. Altered glucose metabolism or associated changes in the pancreas, eye, kidney and adipose tissue were not identified in a 27-week repeat-dose toxicology study in rats that were mature at the beginning of the study and in dogs in repeat-dose toxicology studies up to 39 weeks duration. Toxicities in teeth independent of altered glucose metabolism were observed in rats. Administration of 100 mg/kg palbociclib for 27 weeks (approximately 15 times the adult human exposure [AUC] at the recommended dose) resulted in abnormalities in growing incisor teeth (discolored, ameloblast degeneration/necrosis, mononuclear cell infiltrate). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use
No overall differences in safety or effectiveness of Palbociclib were observed between these patients and younger patients.

Hepatic Impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of Palbociclib is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

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).
The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

4.7. Effects on Ability to Drive and Use Machines
Palbociclib has minor influence on the ability to drive and use machines. However, Palbociclib may cause fatigue and patients should exercise caution when driving or using machines.

4.8. Undesirable Effects
The 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]	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*			
Stomatitisg	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	93 (10.7)	0 (0.0)	0 (0.0)
Uncommon			
Cutaneous lupus erythematosus*	1 (0.1)	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 (ADR) identified post-marketing.
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.
i ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial Lung Disease (narrow).

Table 5. Laboratory abnormalities observed in pooled dataset from 3 randomised studies (N=872)

	Palbociclib plus letrozole or fulvestrant			Comparator arms*		
Laboratory abnormalities	**All grades %**	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
WBC decreased	97.4	41.8	1.0	26.2	0.2	0.2
Neutrophils decreased	95.6	57.5	11.7	17.0	0.9	0.6
Anaemia	80.1	5.6	N/A	42.1	2.3	N/A
Platelets decreased	65.2	1.8	0.5	13.2	0.2	0.0
AST increased	55.5	3.9	0.0	43.3	2.1	0.0
ALT increased	46.1	2.5	0.1	33.2	0.4	0.0

WBC-white blood cells; AST-aspartate aminotransferase; ALT-alanine aminotransferase; N- number of patients; N/A-not applicable.
Note: Laboratory results are graded according to the NCI CTCAE version 4.0 severity grade.
*letrozole or fulvestrant

Description of selected adverse reactions
Overall, neutropenia of any grade was reported in 716 (82.1%) patients receiving Palbociclib regardless of the combination, with Grade 3 neutropenia being reported in 500 (57.3%) patients, and Grade 4 neutropenia being reported in 97 (11.1 %) patients.

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.

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 across the overall clinical programme.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on +91- 40 38265227 **(Direct line); +91 7331134745 (WhatApp)**. By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose
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. Mechanism of action
Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream 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.

Pharmacodynamic effects
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**
Absorption
The maximum observed concentration (C_{max}) of palbociclib is generally observed between 4 to 12 hours (time to reach maximum concentration, T_{max}) following oral administration of Palbociclib tablets. The mean absolute bioavailability of Palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulated with a median accumulation ratio of 2.4 (range 1.5 to 4.2).

Food Effect: The area under the concentration-time curve from zero to infinity (AUC) and C of palbociclib increased by 22% and 26%, respectively, when Palbociclib tablets were given with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), and by 9% and 10%, respectively, when Palbociclib tablets were given with a moderate fat, standard-calorie meal (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively), compared to Palbociclib tablets given under overnight fasted conditions.

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 (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. The geometric mean apparent volume of distribution (V /F) was 2583 L with a coefficient of variation (CV) of 26%.

Metabolism
In vitro and *in vivo* studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [^{14}C]palbociclib to humans, the primary metabolic pathways for palbociclib involved oxidation and 14sulfonation, 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/Excretion
The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/hr (29% CV), and the mean (± standard deviation) plasma elimination half-life was 29 (±5) hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{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.

6. NONCLINICAL PROPERTIES
6.1. **Carcinogenesis, Mutagenesis, Impairment of Fertility**
Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Oral administration of palbociclib for 2 years resulted in an increased incidence of microglial cell tumors in the central nervous system of male rats at a dose of 30 mg/kg/day (approximately 8 times the human clinical exposure based on AUC). There were no neoplastic findings in female rats at doses up to 200 mg/kg/day (approximately 5 times the human clinical exposure based on AUC). Oral administration of palbociclib to male and female rasH2 transgenic mice for 6 months did not result in increased incidence of neoplasms at doses up to 60 mg/kg/day.

Palbociclib was aneugenic in Chinese Hamster Ovary cells in vitro and in the bone marrow of male rats at doses ≥100 mg/kg/day for 3 weeks. Palbociclib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in the in vitro human lymphocyte chromosome aberration assay.

In a fertility study in female rats, palbociclib did not affect mating or fertility at any dose up to 300 mg/kg/day (approximately 4 times human clinical exposure based on AUC) and no adverse effects were observed in the 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 6 times and similar to human exposure [AUC], at the recommended dose, respectively).

The adverse effects of palbociclib on male reproductive function and fertility were observed in the repeat-dose toxicology studies in rats and dogs and a male fertility study in rats. In repeat-dose toxicology studies, palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle at ≥30 mg/kg/day in rats and ≥0.2 mg/kg/day in dogs included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, and decreased secretion. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. These doses in rats and dogs resulted in approximately ≥10 and 0.1 times, respectively, the exposure [AUC] in humans at the recommended dose. In the fertility and early embryonic development study in male rats, palbociclib caused no effects on mating but resulted in a slight decrease in fertility in association with lower sperm motility and density at 100 mg/kg/day with projected exposure levels [AUC] of 20 times the exposure in humans at the recommended dose.

7. PHARMACEUTICAL PARTICULARS

7.1. Incompatibilities
Not applicable.

7.2. Packing Information
7's & 10's blister pack.

7.3. Storage and Handling Information
Do not store above 30°C

KEEP OUT OF REACH FOR CHILDREN

8. PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).
Myelosuppression/Infection
Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness, or any increased tendency to bleed and/or to bruise.

Interstitial Lung Disease/Pneumonitis
Advise patients to immediately report new or worsening respiratory symptoms.

Drug Interactions
Grapefruit may interact with Palbociclib. Patients should not consume grapefruit products while on treatment with Palbociclib.

Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

Dosing and Administration
Inform patients that Palbociclib tablets may be taken with or without food.

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 tablets should be swallowed whole (do not chew, crush, or split them prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with Palbociclib should also be treated with LHRH agonists.

Pregnancy, Lactation, and Infertility
Embryo-Fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with Palbociclib therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Palbociclib and for at least 3 months after the last dose.

Lactation: Advise women not to breastfeed during treatment with Palbociclib and for 3 weeks after the last dose.

Infertility: Inform males of reproductive potential that Palbociclib may cause infertility and to consider sperm preservation before taking Palbociclib.

9. DETAILS OF MANUFACTURER
MSN Laboratories Private Limited,
Formulation Division,
Unit II, Survey No. 1277 & 1319 to 1324,
Nandigama (Village and Mandal),
Rangareddy District, Pin Code: 509228,
Telangana, India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
M.L.No.: 5/MN/TS/2014/F/G, 26/08/2019

11. DATE OF REVISION
Nov 2022

C030478-00