

SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT

PALBIS 100 (Palbociclib capsules 100 mg)

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains

Palbociclib100 mg.

Excipient with known effect;

Lactose monohydrate

For list of excipients see section 6.1

3.PHARMACEUTICAL FORM

Dosage Form: Capsules

Pink Opaque cap and White Opaque body size '1' hard gelatin capsules imprinted with 'H' on cap and 'PAB 100' on body, filled with Pale yellow to yellow color granular powder.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant in patients with disease progression following endocrine therapy.

4.2 Posology and method of administration

The recommended dose of Palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food.

Administer the recommended dose of an aromatase inhibitor when given with Palbociclib. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

When given with Palbociclib, the recommended dose of fulvestrant is 500

mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant. Patients should be encouraged to take their dose of Palbociclib at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Palbociclib capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

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

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

4.2.1 Dose Modification

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

Table 1. Recommended Dose Modification for Adverse Reactions

Dose Level	Dose
Recommended starting 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.

Table 2. Dose Modification and Management – Hematologic Toxicities

Monitor complete blood counts 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, 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	<u>Day 1 of cycle:</u> Withhold Palbociclib, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2 , start the next cycle at the <i>same dose</i> . <u>Day 15 of first 2 cycles:</u> If Grade 3 on Day 15, continue Palbociclib at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia with fever ≥ 38.5 °C and/or infection	<u>At any time:</u> Withhold Palbociclib until recovery to Grade ≤ 2 . Resume at the <i>next lower dose</i> .
Grade 4	<u>At any time:</u> Withhold Palbociclib until recovery to Grade ≤ 2 . Resume at the <i>next lower dose</i> .

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.

*Table applies to all hematologic adverse reactions except lymphopenia (Unless associated with clinical events, e.g., opportunistic infections).

#Absolute neutrophil count (ANC): Grade 1: ANC $< \text{LLN} - 1500/\text{mm}$; Grade 2: ANC $1000 - <1500/\text{mm}$; Grade 3: ANC $500 - <1000/\text{mm}$; Grade 4: ANC $<500/\text{mm}$.

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

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold until symptoms resolve to: Grade ≤ 1 ; Grade ≤ 2 (if not considered a safety risk for the patient) Resume at the <i>next lower dose</i> .

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.

Refer to the Full Prescribing Information for co administered endocrine

therapy dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

Dose Modifications for Use With Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be co-administered 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.

Dose Modifications for Hepatic Impairment

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

4.3 Contraindications

None

4.4 Special warnings and precautions for use

4.4.1 Neutropenia

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 with an incidence of 0% and PALOMA-3 with an incidence of 83%. A Grade ≥ 3 decrease in neutrophil counts was reported in 66% of patients receiving Palbociclib plus letrozole in PALOMA-2 and 66% of patients receiving Palbociclib plus fulvestrant in PALOMA-3. In PALOMA-2 and PALOMA-3, 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 PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Physicians should inform patients to promptly report any episodes of fever.

4.4.2 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.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of Palbociclib-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4 and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post marketing 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.

4.4.3 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 Interaction with other medicinal products and other forms of interaction

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, Palbociclib is a time-dependent inhibitor of

CYP3A.Agents That May Increase Palbociclib Plasma Concentrations Effect of CYP3A Inhibitors

Co-administration 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

Co-administration 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

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 Fertility, pregnancy and lactation Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Palbociclib can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of Palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥ 4 times the human clinical exposure based on AUC. Advise pregnant women of the potential

risk to a fetus.

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

There is no information regarding the presence of Palbociclib in human milk, its effects on milk production, or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from

Palbociclib, 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

Of 444 patients who received Palbociclib in PALOMA-2, 181 patients (41%) were ≥ 65 years of age and 48 patients (11%) were ≥ 75 years of age. Of 347 patients who received Palbociclib in PALOMA-3, 86 patients (25%) were ≥ 65 years of age and 27 patients (8%) were ≥ 75 years of age. No overall differences in safety or effectiveness of Palbociclib were observed between these patients and younger patients.

Hepatic Impairment

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

Review the Full Prescribing Information for the aromatase inhibitor or fulvestrant for dose

modifications related to hepatic impairment.

Renal Impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment ($\text{CrCl} > 15 \text{ mL/min}$). Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUC_{INF}) increased by 39%, 42%, and 31% with mild ($60 \text{ mL/min} \leq \text{CrCl}$

$< 90 \text{ mL/min}$), moderate ($30 \text{ mL/min} \leq \text{CrCl} < 60 \text{ mL/min}$), and severe ($\text{CrCl} < 30 \text{ mL/min}$) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neutropenia
- ILD/Pneumonitis

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

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

Clinical Studies Experience

Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

PALOMA-2: Palbociclib plus Letrozole

Patients with estrogen receptor (ER)-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy

The safety of Palbociclib (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in PALOMA-2. The data described below reflect exposure to Palbociclib in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of albociclib plus letrozole in PALOMA-2. The median duration of treatment for Palbociclib plus

letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was

13.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients

Receiving Palbociclib plus letrozole. No dose reduction was allowed for letrozole in PALOMA-2. Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving Palbociclib plus letrozole and in 13 of 222 (5.9%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving Palbociclib plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions ($\geq 10\%$) of any grade reported in patients in the Palbociclib plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia. The most frequently reported Grade ≥ 3 adverse reactions ($\geq 5\%$) in patients receiving Palbociclib plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse reactions ($\geq 10\%$) reported in patients who received Palbociclib

plus letrozole or placebo plus letrozole in PALOMA-2 are listed in Table 4.

Table 4. Adverse Reactions (≥10%) in PALOMA-2

		Palbociclib plus Letrozole (N=444)		Placebo plus Letrozole (N=222)		
Adverse Reaction	All Grade s %	Grade 3 %	Grade 4 %	All Grade s %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections*	60†	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33§	N/A	N/A	16¶	N/A	N/A
Rash#	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable;

*Infections includes all reported preferred terms (PTs) that are part

of the System Organ Class Infections and infestations.

†Most common infections ($\geq 1\%$) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.

‡Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

§ Grade 1 events – 30%; Grade 2 events – 3%

¶ Grade 1 events – 15%; Grade 2 events – 1%.

#Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of $<10.0\%$ of patients receiving Palbociclib plus letrozole in PALOMA-2 included alanine aminotransferase increased (9.9%), aspartate aminotransferase increased (9.7%), epistaxis (9.2%), lacrimation increased (5.6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

Table 5. Laboratory Abnormalities in PALOMA-2

Adverse Reaction	Palbociclib plus Letrozole (N=444)		Placebo plus Letrozole (N=222)			
	All Grade s %	Grade 3 %	Grade 4 %	All Grade s %	Grade 3 %	Grade 4 %
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0

Alanine aminotransferase increased	43	2	<1	30	0	0
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N=number of patients; WBC=white blood cells.

PALOMA-3: Palbociclib plus Fulvestrant

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of Palbociclib (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in PALOMA-3. The data described below reflect exposure to Palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least

1 dose of Palbociclib plus fulvestrant in PALOMA-3. The median duration of treatment for Palbociclib plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving Palbociclib plus fulvestrant. No dose reduction was allowed for fulvestrant in PALOMA-3. Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving Palbociclib plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving Palbociclib plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%). The most common adverse reactions ($\geq 10\%$) of any grade reported in patients in the Palbociclib plus fulvestrant arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade ≥ 3 adverse reactions ($\geq 5\%$) in patients receiving Palbociclib plus fulvestrant in descending frequency were neutropenia and leukopenia.

Table 6. Adverse Reactions (≥10%) in PALOMA-3

Adverse Reaction	Palbociclib plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Infections and infestations						
Infections*	47†	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis‡	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18§	N/A	N/A	16¶	N/A	N/A
Rash#	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Pyrexia	17	2	0	12	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse

Events; N=number of patients; N/A=not applicable;

*Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

†Most common infections (≥1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral,

respiratory tract infection, respiratory tract infection viral, and folliculitis.

‡Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

§ Grade 1 events – 30%; Grade 2 events – 3%

¶ Grade 1 events – 15%; Grade 2 events – 1%.

#Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption. Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving Palbociclib plus fulvestrant in PALOMA-3 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Table 7. Laboratory Abnormalities in PALOMA-3

Laboratory Abnormality	Palbociclib plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grade s %	Grade 3 %	Grade 4 %	All Grade s %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

N=number of patients; WBC=white blood cells.

CLINICAL STUDIES

PALOMA-2: Palbociclib plus Letrozole

Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine-based therapy

PALOMA-2 was an international, randomized, double-blind, parallel-group, multicenter study of Palbociclib plus letrozole versus placebo plus letrozole conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. A total of 666 patients were randomized 2:1 to Palbociclib plus letrozole or placebo plus letrozole. Randomization was stratified by disease site (visceral versus non-visceral), disease-free interval (de novo metastatic versus ≤ 12 months from the end of adjuvant treatment to disease recurrence versus > 12 months from the end of adjuvant treatment to disease recurrence), and nature of prior (neo) adjuvant anticancer therapies (prior hormonal therapies versus no prior hormonal therapy). Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Patients received study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by the investigator according to RECIST Version 1.1 and overall survival (OS).

Patients enrolled in this study had a median age of 62 years (range 28 to 89). The majority of patients were White (78%), and most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (98%). Forty-eight percent of patients had received chemotherapy and 56% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Thirty-seven percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (97%) had metastatic disease. Twenty-three percent of patients had bone only disease, and 49% of

patients had visceral disease.

Major efficacy results from PALOMA-2 are summarized in Table 8 and Figure 1. Consistent results were observed across patient subgroups of disease-free interval (DFI), disease site, and prior therapy. The treatment effect of the combination on PFS was also supported by an independent review of radiographs. Based on the prespecified final OS analysis conducted after 435 events, OS was not statistically significant.

Table 8. Efficacy Results – PALOMA-2

	Palbociclib plus Letrozole	Placebo plus Letrozole
Progression-free survival for ITT (investigator assessment)	N=444	N=222
Number of PFS events (%)	194 (43.7)	137 (61.7)
Median progression- free survival (months, 95% CI)	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio (95% CI) and pvalue	0.576 (0.463, 0.718)*, p<0.0001†	
Objective Response for patients with measurable disease (investigator assessment)	N=338	N=171
Objective response rate (%,	55.3 (49.9, 60.7)	44.4 (36.9, 52.2)

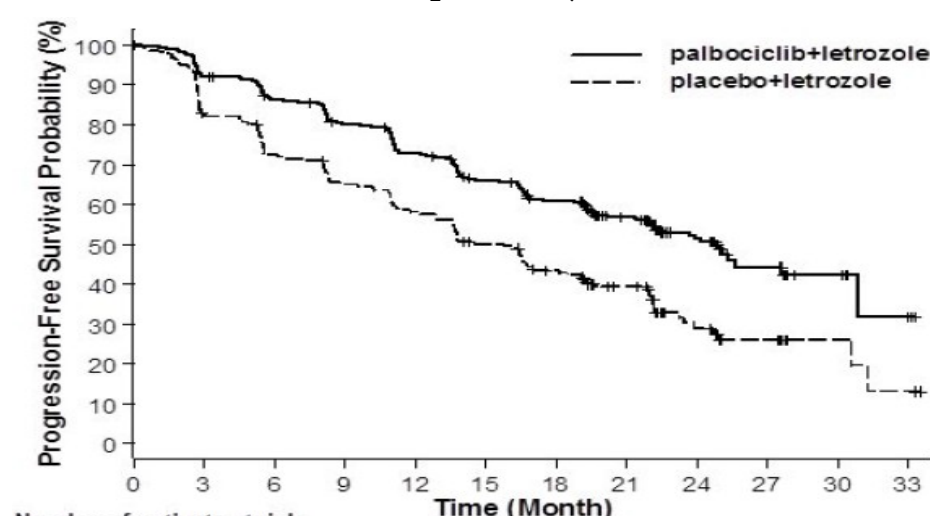
CI=confidence interval; ITT=Intent-to-Treat; N=number of patients; NE=not estimable; OS=overall survival; PFS=progression-free survival.

*Cox proportional hazards model stratified by disease site (visceral vs. nonvisceral) per randomization.

†Stratified log-rank test one-sided p-value.

‡Response is based on confirmed responses.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival – PALOMA-2 (Investigator Assessment, Intent-to-Treat Population)



Number of patients at risk

95% CI)		
Overall survival for ITT	N=444	N=222
Number of OS events (%)	287 (64.6)	148 (66.7)
Median OS (months, 95% CI)	53.8 (49.8, 59.2)	49.8 (42.3, 56.4)
Hazard ratio (95% CI) and p-value	0.921 (0.755, 1.124) *, p=0.2087†	

PAL+LET	444	395	360	328	295	263	238	154	69	29	10	2
PBO+LET	222	171	148	131	116	98	81	54	22	12	4	2

LET=letrozole; PAL=Palbociclib; PBO=placebo.

PALOMA-3: Palbociclib plus Fulvestrant

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

PALOMA-3 was an international, randomized, double-blind, parallel group, multicenter study of Palbociclib plus fulvestrant versus placebo plus fulvestrant conducted in women

with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. A total of 521 pre/postmenopausal women were randomized 2:1 to Palbociclib plus fulvestrant or placebo plus fulvestrant and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of PALOMA-3. Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients on study were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy, and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS and final OS from PALOMA-3 are summarized in Table 9. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively. Consistent PFS results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. After a median follow-up time of 45 months, the final OS results were not statistically significant.

Table 9. Efficacy Results – PALOMA-3

	Palbociclib plus Fulvestrant	Placebo plus Fulvestra nt
Progression-free survival for ITT (investigator assessment)	N=347	N=174
Number of PFS events (%)	145 (41.8)	114 (65.5)
Median progression-free survival (months, 95% CI)	9.5 (9.2, 11.0)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and pvalue	0.461 (0.360, 0.591), p<0.0001	
Objective Response for patients with measurable disease (investigator assessment)	N=267	N=138
Objective response rate (%; 95% CI)	24.6 (19.6, 30.2)	10.9 (6.2, 17.3)
Overall survival for ITT	N=347	N=174
Number of OS events (%)	201 (57.9)	148 (66.7)
Median OS (months, 95% CI)	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value	0.814 (0.644, 1.029), p=0.0857†‡	

CI=confidence interval; ITT=Intent-to-Treat;

N=number of patients; OS=overall survival;

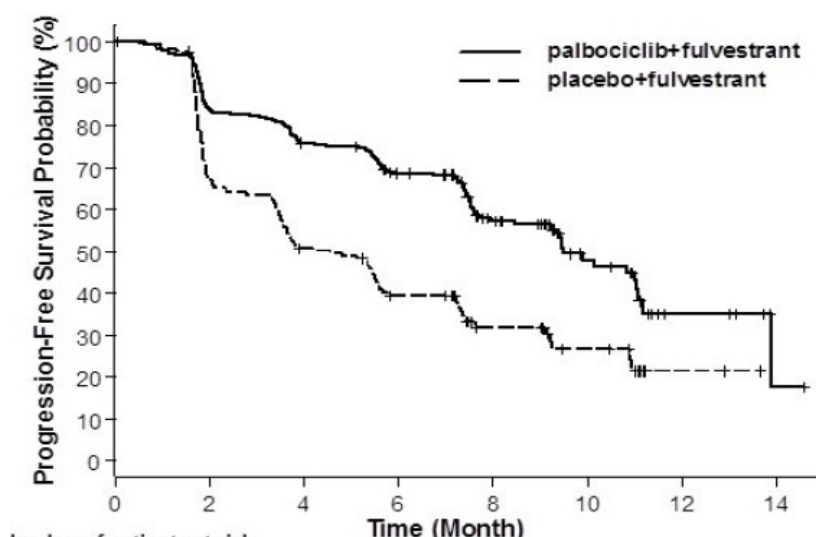
PFS=progression-free survival.

*Responses are based on confirmed responses.

†Not statistically significant at the pre-specified 2-sided alpha level of 0.047.

‡2-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomization.

Figure 2. Kaplan-Meier Plot of Progression-Free Survival – PALOMA-3 (Investigator Assessment, Intent-to-Treat Population)

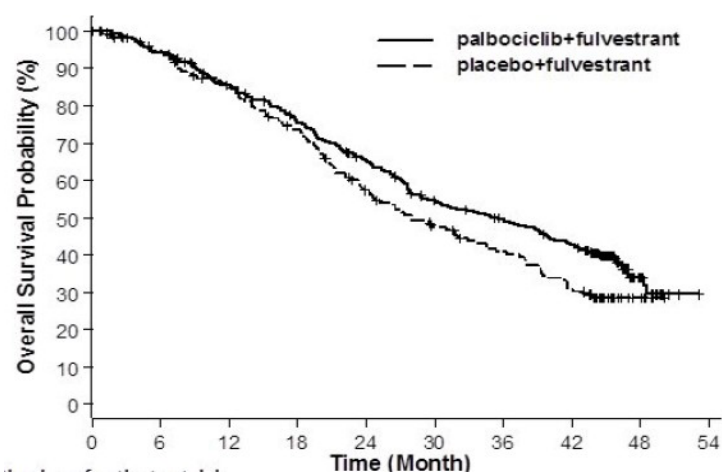


Number of patients at risk

PAL+FUL	347	281	247	202	91	32	7	1
PBO+FUL	174	112	83	59	22	13	2	0

FUL=fulvestrant; PAL=Palbociclib; PBO=placebo

Figure 3. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) PALOMA-3



Number of patients at risk

PAL+FUL	347	286	247	209	165	32	7	1
PBO+FUL	174	135	115	86	68	13	2	0

FUL=fulvestrant; PAL=Palbociclib; PBO=placebo.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of Palbociclib. Because these reactions are reported voluntarily from a

population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory Disorders: Interstitial lung disease (ILD)/non-infectious pneumonitis
Skin and Subcutaneous Tissue Disorders: Palmar-plantar erythrodysesthesia syndrome (PPES)

Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer

Based on limited data from post marketing reports and electronic health records, the safety profile for men treated with Palbociclib is consistent with the safety profile in women treated with Palbociclib. **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. Healthcare professionals are asked to report any suspected adverse reactions via ADR reporting tool of health authority; search for Adverse Reactions Reporting Tool in the Google Play Store.

5. Pharmacological properties Pharmacotherapeutic group:

Antineoplastic Agent.

Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

ATC code: L01XE33

5.1 Pharmacodynamics properties

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.

Switching from clopidogrel 75 mg to ticagrelor 90 mg twice daily results in an absolute IPA.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of Palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

Absorption

The mean maximum observed concentration (C_{max}) of Palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration, T_{max}) following oral administration. The mean absolute bioavailability of Palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and 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: Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the Palbociclib exposure in this small subset of the population, but did not alter Palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the intersubject variability of Palbociclib exposure, which supports administration of Palbociclib with food. Compared to Palbociclib given under overnight fasted conditions, the population average area under the concentration-time curve from zero to infinity (AUC_{INF}) and C_{max} of Palbociclib increased by 21% and 38%, respectively, when given with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), by 12% and 27%, respectively, when given with low-fat, low-calorie food (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate, and fat, respectively), and by 13% and 24%, respectively, when moderate-fat, standard calorie food (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively) was given 1 hour before and 2 hours after Palbociclib dosing.

Distribution

Binding of Palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence over the concentration range of 500 mg/mL to 5000 mg/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_z/F) was 2583 L with a coefficient of variation (CV) of 26%.

Metabolism

In vitro and in vivo studies indicated that Palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg

dose of [¹⁴C] Palbociclib to humans, the primary metabolic pathways for Palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways.

Palbociclib was the major circulating drug-derived entity in plasma (23%). The major circulating metabolite was a glucuronide conjugate of Palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of Palbociclib was the major drug-related component, accounting for 26% of the administered dose. In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant SULT enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of Palbociclib.

Elimination

The geometric mean apparent oral clearance (CL/F) of Palbociclib was 63.1 L/hr (29% CV), and the mean (± standard deviation) plasma elimination half-life was 29 (±5) hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [¹⁴C] Palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. The majority of the material was excreted as Metabolites.

Age, Gender, and Body Weight

Paediatric population

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 to 123 kg), gender had no effect on the exposure of Palbociclib, and age and body weight had no clinically important effect on the exposure of Palbociclib.

Pediatric Population

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

Hepatic Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic impairment indicate that Palbociclib unbound AUC decreased 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. Palbociclib unbound C increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin $\leq$ ULN and AST $>$ ULN, or total bilirubin >1.0 to $1.5 \times$ ULN and any AST), mild hepatic impairment had no effect on the exposure of Palbociclib, further supporting the findings from the dedicated hepatic impairment study.

Renal Impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that Palbociclib AUC increased by 39%, 42%, and 31% with mild ($60 \text{ mL/min} \leq \text{CrCl} < 90 \text{ mL/min}$), moderate ($30 \text{ mL/min} \leq \text{CrCl} < 60 \text{ mL/min}$), and severe ($\text{CrCl} < 30 \text{ mL/min}$) renal impairment, respectively, relative to subjects with normal renal function. Peak Palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. In addition, based on a population pharmacokinetic analysis that included 183 patients where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the exposure of Palbociclib. The pharmacokinetics of Palbociclib have not been studied in patients requiring hemodialysis.

Drug Interactions

In vitro data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. 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.

CYP3A Inhibitors: Data from a drug interaction trial in healthy subjects (N=12) indicate that co-administration of multiple 200 mg daily doses of

itraconazole with a single 125 mg Palbociclib dose increased palbociclib AUC and the C_{max} by approximately 87% and 34%, respectively, relative to a single 125 mg Palbociclib dose given alone.

CYP3A Inducers: Data from a drug interaction trial in healthy subjects (N=15) indicate that co-administration of multiple 600 mg daily doses of rifampin, a strong CYP3A inducer, with a single 125 mg Palbociclib dose decreased palbociclib AUC and C_{max} by 85% and 70%, respectively, relative to a single 125 mg Palbociclib dose given alone. Data from a drug interaction trial in healthy subjects (N=14) indicate that co-administration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg Palbociclib dose decreased palbociclib AUC and C_{max} by 32% and 11%, respectively, relative to a single 125 mg Palbociclib dose given alone.

CYP3A Substrates: Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In a drug interaction trial in healthy subjects (N=26), co-administration of midazolam with multiple doses of Palbociclib increased the midazolam AUC and the C_{max} values by 61% and 37%, respectively, as compared to administration of midazolam alone. **Gastric pH Elevating Medications:** In a drug interaction trial in healthy subjects, 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 (13% decrease), when compared to a single 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 agents 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 dose of Palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC and C_{max} by 62% and 80%, respectively, when compared to a single dose of Palbociclib administered alone.

Letrozole: Data from a clinical trial in patients with breast cancer showed that there was no drug

interaction between palbociclib and letrozole when the 2 drugs were coadministered.

Fulvestrant: Data from a clinical trial in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the 2 drugs were co-administered. **Goserelin:** Data from a clinical trial in patients with breast cancer showed that there was

no clinically relevant drug interaction between palbociclib and goserelin when the 2 drugs were coadministered.

Anastrozole or Exemestane: No clinical data are available to evaluate drug interactions

between anastrozole or exemestane and palbociclib. A clinically significant drug interaction between anastrozole or exemestane and palbociclib is not expected based on analyses of the effects of anastrozole, exemestane and palbociclib on or by metabolic pathways or transporter systems.

Effect of Palbociclib on Transporters: In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1, OATP1B3 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-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) in the gastrointestinal tract at the proposed dose.

Effect of Transporters on Palbociclib: 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.

NONCLINICAL TOXICOLOGY

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.

6. Pharmaceutical Particulars:

6.1 List of excipients:

Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells.

Hard Gelatin Capsule Shell composition: Gelatin, Titanium dioxide, Iron

oxide red and water.

Composition of Black SW-9008/SW-9009 printing ink: Shellac, Dehydrate alcohol, 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

Store below 30°C

6.5 Nature and contents of container

21's HDPE Container

6.6 Instructions for use, handling and disposal

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

7 . MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE

M/S. HETERO LABS LIMITED,

UNIT-V Sy.No.439, 440, 441 & 458, TSIIC

Formulation SEZ, Polepalle Village, Jadcherla Mandal,

Mahabubnagar District, Pincode 509301, Telangana state, India

8. MARKETING AUTHORISATION NUMBER

H2026/CTD12934/26735

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

18/02/2026

10. DATE OF REVISION OF THE TEXT

18/02/2026