## 1. NAME OF THE MEDICINAL PRODUCT

PALBOCICLIB SANDOZ CAPSULE 75MG
PALBOCICLIB SANDOZ CAPSULE 100MG
PALBOCICLIB SANDOZ CAPSULE 125MG

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Palbociclib Sandoz Capsule 75mg
Each capsule contains 75mg of Palbociclib.

Palbociclib Sandoz Capsule 100mg
Each capsule contains 100mg of Palbociclib.

Palbociclib Sandoz Capsule 125mg
Each capsule contains 125mg of Palbociclib.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule.

Palbociclib Sandoz Capsule 75mg
Yellow colored powder in hard gelatin, capsule size '2', white opaque body and white opaque cap, imprinted in black with two 320° band on cap and “75” on body. Should be free from physical defects.

Palbociclib Sandoz Capsule 100mg
Yellow colored powder in hard gelatin, capsule size '1', Swedish orange opaque body and Swedish orange opaque cap, imprinted in black with two 320° band on cap and “100” on body. Should be free from physical defects.

Palbociclib Sandoz Capsule 125mg
Yellow colored powder in hard gelatin, capsule size '0', white opaque body and Swedish orange opaque cap, imprinted in black with two 320° band on cap and “125” on body. Should be free from physical defects.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Palbociclib is indicated for the treatment of 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 (Schedule 3/1) to comprise a complete cycle of 28 days.

When co-administered with palbociclib, the aromatase inhibitor should be administered according to the dose reported in the approved prescribing information.

When co-administered 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 full prescribing information of fulvestrant.

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

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Palbociclib Sandoz 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, pre/perimenopausal women treated with the combination palbociclib plus aromatase inhibitor/fulvestrant should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

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

**Dose modifications**

Dose modification of palbociclib 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 Section 4.4 and Section 4.8).

**Table 1. Palbociclib 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[a] |

[a] If further dose reduction below 75 mg/day is required, discontinue the treatment.

**Table 2. Palbociclib Dose Modification and Management – Hematologic Toxicities[a]**

| 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.<br><br>For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated. | |
|---|---|
| **CTCAE Grade** | **Dose Modifications** |
| Grade 1 or 2 | No dose adjustment is required. |

| | |
|---|---|
| Grade 3[a] | Day 1 of cycle:<br>Withhold palbociclib, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the *same dose*.<br><br>Day 15 of first 2 cycles:<br>Continue palbociclib at the *current dose* to complete cycle and repeat complete blood count on Day 22.<br><br>Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of the subsequent cycles. |
| Grade 3 ANC[b] (<1,000 to 500/mm$^3$) + fever ≥38.5°C and/or infection | At any time:<br>Withhold palbociclib until recovery to Grade ≤2.<br>Resume at the *next lower dose*. |
| Grade 4[a] | At any time:<br>Withhold palbociclib until recovery to Grade ≤2.<br>Resume at the *next lower dose*. |

Grading according to CTCAE 4.0 (Grade 1: ANC <LLN - 1500/mm$^3$; Grade 2: ANC 1000 - <1500/mm$^3$; Grade 3: ANC 500 - <1000/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 hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

[b] ANC: Grade 1: ANC <LLN - 1500/mm$^3$; Grade 2: ANC 1000 - <1500/mm$^3$; Grade 3: ANC 500 - <1000/mm$^3$; Grade 4: ANC <500/mm$^3$.

**Table 3. Palbociclib 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 medical treatment) | Withhold until symptoms resolve to:<br>• Grade ≤1;<br>• Grade ≤2 (if not considered a safety risk for the patient)<br>Resume at the *next lower dose*. |

Grading according to CTCAE 4.0

CTCAE=Common Terminology Criteria for Adverse Events.

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

Permanently discontinue palbociclib 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).

*Pediatric population:* The safety and efficacy of palbociclib in children and adolescents <18 years of age have not been established.

*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 on Schedule 3/1 (see 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 hemodialysis to provide any dosing recommendation in this patient population (see Section 5.2).

**4.3. Contraindications**

None

**4.4. Special warnings and precautions for use**

**Neutropenia**

Decreased neutrophil counts have been observed very commonly in clinical studies with palbociclib. In patients receiving palbociclib in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 (ANC 500-<1000/mm$^3$) and Grade 4 (ANC <500/mm$^3$) decreased neutrophil counts were reported in 56.1% and 10.6% of patients, respectively (see Section 4.8).

In PALOMA-1 and PALOMA-2 the median time to first episode of any grade neutropenia was 15 days (range 12-700 days) and 28 days (range 12-854) for Grade ≥3 neutropenia. The median duration of Grade ≥3 neutropenia was 33 days (range 1-534).

In PALOMA-3 the median time to first episode of neutropenia was 15 days (13-317 days) for any grade and 16 days (range 13-587) for Grade ≥3 neutropenia. The median duration for Grade ≥3 neutropenia was 21 days (range 1-167).

An increase in palbociclib exposure has been associated with more severe neutropenia; in Asian subjects, frequency of Grade ≥3 neutropenia is higher than in White subjects (see Section 5.2).

Febrile neutropenia has been reported in 1.6% of patients receiving palbociclib in combination with letrozole in PALOMA-2 and in 0.9% of patients receiving palbociclib in combination with fulvestrant in PALOMA-3. One death due to neutropenic sepsis was reported in PALOMA-3.

Febrile neutropenia has not been reported in PALOMA-1. Febrile neutropenia has been reported in about 2% of patients exposed to palbociclib across the overall clinical program (see Section 4.4).

Monitor complete blood count 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.

Dosing interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed (see Section 4.2).

**Interstitial lung disease/pneumonitis**

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

combination with endocrine therapy.

Across clinical trials, 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 observed in the post-marketing setting (see Section 4.8), 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 ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. Permanently discontinue palbociclib in patients with severe ILD or pneumonitis (see Section 4.2).

**Infections**

Since palbociclib has myelosuppressive properties, it may predispose to infections.

Infections of any grade have been reported at a higher rate in patients treated with palbociclib plus letrozole or fulvestrant (54.7%) compared to patients treated in the respective comparator arms (36.9%). Grades 3 and 4 infections occurred in 4.4% and 0.7%, respectively, in patients treated with palbociclib in either combination compared to patients treated in the respective comparator arms (2.5% and 0%, respectively).

Monitor patients for signs and symptoms of infection and treat as medically appropriate (see Section 4.8).

Physicians should inform patients to promptly report any episodes of fever.

**Pulmonary embolism**

Pulmonary embolism has been reported at a higher rate in patients treated with palbociclib plus letrozole (5%) compared with no cases in patients treated with letrozole alone in Study 1. Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate.

**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

Data from a drug-drug interaction (DDI) study in healthy subjects indicate that co-administration of multiple 200 mg doses of itraconazole with a single 125 mg dose of palbociclib increased palbociclib total exposure area under the plasma concentration-time curve from time zero to infinity ($AUC_{inf}$) and the maximum observed plasma concentration ($C_{max}$) by approximately 87% and 34%, respectively, relative to a single 125 mg dose of palbociclib given alone. The concomitant use of strong CYP3A inhibitors including, but not limited to: amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem,

erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided.

*Agents that may decrease palbociclib plasma concentrations*

Effect of CYP3A inducers

Data from a DDI study in healthy subjects indicate that co-administration of multiple 600 mg doses of rifampin, a strong CYP3A inducer, with a single 125 mg dose of palbociclib decreased palbociclib $AUC_{inf}$ and $C_{max}$ by 85% and 70%, respectively, relative to a single 125 mg dose of palbociclib given alone. Data from a DDI study in healthy subjects 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 $AUC_{inf}$ and $C_{max}$ by 32% and 11%, respectively, relative to a single 125 mg dose of palbociclib given alone.

The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, and St. John's wort, should be avoided.

Co-administration of a moderate CYP3A inducer (modafinil) decreased the plasma exposure of palbociclib in healthy subjects by 32%. Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) can be used concurrently with palbociclib when unavoidable. No dosing adjustments are required.

*Effect of acid reducing agents*

Data from a DDI study in healthy subjects indicated that 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) compared with 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, under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure.

Data from another DDI study in healthy subjects indicated that co-administration of a single dose of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib $AUC_{inf}$ and $C_{max}$ by 62% and 80%, respectively, when compared with a single dose of palbociclib administered alone.

Therefore, palbociclib should be taken with food (see Section 4.2).

*Effects of palbociclib on other drugs*

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

*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.

Letrozole: Data from a clinical study in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 drugs were co-administered.

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

Tamoxifen: Data from a DDI study in healthy male subjects indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when palbociclib was given alone.

*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**

**Fertility**

There were no effects on estrous cycle (female rats) or mating and fertility in rats in non-clinical studies. However, no clinical data have been obtained on fertility in human females. Based on non-clinical safety findings in male reproductive tissues, male fertility may be compromised by treatment with palbociclib (see Section 5.3). Men should consider sperm preservation prior to beginning therapy with palbociclib.

**Women of childbearing potential/pregnancy**

There are no adequate and well-controlled studies using palbociclib in pregnant women. Based on findings in animals and mechanism of action, palbociclib can cause fetal harm when administered to a pregnant woman. In animal studies, palbociclib was fetotoxic at maternally-toxic doses. Palbociclib is not recommended during pregnancy and in women of childbearing potential not using contraception.

Females of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods during therapy and for at least 21 days or 97 days after completing therapy for females and males, respectively.

**Lactation**

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 palbociclib should not breastfeed.

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

No studies on the effects of palbociclib on the ability to drive or operate machinery have been conducted. However, patients experiencing fatigue while taking palbociclib should exercise caution when driving or operating machinery.

**4.8. Undesirable effects**

**Summary of the safety profile**

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

The most common (≥20%) adverse reactions of any grade reported in patients receiving palbociclib in randomized clinical studies were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, diarrhoea, alopecia, and thrombocytopenia. The most common (≥2%) Grade ≥3 adverse reactions of palbociclib were neutropenia, leukopenia, infections, anaemia, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased.

Dose reductions or dose modifications due to any adverse reaction occurred in 38.4% of patients receiving palbociclib in randomized clinical studies regardless of the combination.

Permanent discontinuation due to an adverse reaction occurred in 5.2% of patients receiving palbociclib in randomized clinical studies regardless of the combination.

Tabulated list of adverse reactions

Table 4 reports the adverse reactions from the pooled dataset of 3 randomized studies. The median duration of palbociclib treatment across the pooled dataset at the time of the final OS analysis was 14.8 months. 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 Randomized Studies (N=872)**

| **System Organ Class**<br>**Frequency**<br>**Preferred Term[a]** | **All Grades n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** |
|---|---|---|---|
| **Infections and infestations**<br>*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) |
| **Vascular disorders** | | | |
| *Common* | | | |
| Venous thromboembolism[*,j] | 28 (3.2) | 11 (1.3) | 7 (0.8) |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| *Common* | | | |
| Epistaxis | 77 (8.8) | 0 (0.0) | 0 (0.0) |
| ILD/pneumonitis[*,i] | 12 (1.4) | 1 (0.1) | 0 (0.0) |
| **Gastrointestinal disorders** | | | |
| *Very common* | | | |
| Stomatitis[g] | 264 (30.3) | 8 (0.9) | 0 (0.0) |
| Nausea | 314 (36.0) | 5 (0.6) | 0 (0.0) |
| Diarrhoea | 238 (27.3) | 9 (1.0) | 0 (0.0) |
| Vomiting | 165 (18.9) | 6 (0.7) | 0 (0.0) |
| **Skin and subcutaneous tissue disorders** | | | |
| *Very common* | | | |
| Rash[h] | 158 (18.1) | 7 (0.8) | 0 (0.0) |
| Alopecia | 234 (26.8) | N/A | N/A |
| Dry skin | 93 (10.7) | 0 (0.0) | 0 (0.0) |
| *Common* | | | |
| Palmar-plantar erythrodysaesthesia syndrome[*] | 16 (1.8) | 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 MedDRA25.1.

[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 Standardized MedDRA Query Interstitial Lung Disease (narrow).

[j] 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 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 (see Table 4).

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

Febrile neutropenia has been reported in 0.9% 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.

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.

### 4.9. Overdose

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

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

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

Palbociclib is taken orally and is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into
S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high efficacy against luminal breast cancers, particularly estrogen receptor (ER)-positive breast cancers. Mechanistic analyses revealed that the combination of palbociclib with anti-estrogen agents enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signaling and growth arrest. The enhanced growth arrest of the ER-positive breast cancer cell lines treated with palbociclib and anti-estrogen agents 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 signaling and dose-dependent tumor growth. This supports the contribution of senescence-associated growth arrest as a mechanism associated with the antitumor efficacy of combined palbociclib/ER antagonist in ER-positive breast cancer models.

In the presence or absence of an anti-estrogen, palbociclib-treated bone marrow cells did not become senescent and resumed proliferation following palbociclib withdrawal, consistent with pharmacologic quiescence. The *in vitro* breast cancer cells, conversely, became senescent following palbociclib or anti-estrogen treatment with additive effects in combination and remained arrested in the presence of anti-estrogen.

*Clinical trial efficacy*

*Study 1: Randomized Phase 1/2 study of palbociclib in combination with letrozole (PALOMA-1)*

The efficacy of palbociclib was evaluated in a randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in post-menopausal women with ER-positive, HER2-negative advanced breast cancer who did not receive previous systemic treatment for their advanced disease (PALOMA-1).

The study was comprised of a limited Phase 1 portion (N = 12), designed to confirm the safety and tolerability of the combination palbociclib plus letrozole, followed by a randomized Phase 2 portion (N = 165), designed to evaluate the efficacy and safety of palbociclib in combination with letrozole compared with letrozole alone in the first-line treatment of post-menopausal women with ER-positive, HER2-negative advanced breast cancer.

Randomization was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or *de novo* advanced disease).

The patient demographic and baseline characteristics were generally balanced between the study arms in terms of age, race, disease sites, stage, and prior therapies.

The primary endpoint of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

The median PFS (mPFS) for patients in the palbociclib plus letrozole arm was 20.2 months (95% confidence interval [CI]: 13.8, 27.5) and 10.2 months (95% CI: 5.7, 12.6) for patients in the letrozole-alone arm. The observed hazard ratio (HR) was 0.488 (95% CI: 0.319, 0.748) in favor of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of 0.0004.

*Study 2 - Randomized Phase 3 Study of palbociclib in combination with letrozole (PALOMA-2)*

The efficacy of palbociclib in combination with letrozole versus letrozole plus placebo was evaluated in an international, randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in women with ER-positive, HER2-negative advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer who had not received prior systemic treatment for their advanced disease.

A total of 666 post-menopausal women were randomized 2:1 to either the palbociclib plus letrozole arm or to the placebo plus letrozole arm and were stratified by site of disease (visceral, non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (*de novo* metastatic, ≤12 months from the end of adjuvant treatment to disease recurrence, >12 months from the end of adjuvant treatment to disease recurrence), and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy, no prior hormonal therapy). Patients with advanced symptomatic visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

Patients continued to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Patients were well matched for baseline demographics and disease characteristics between the palbociclib plus letrozole arm and the placebo plus letrozole arm. The median age of patients enrolled in this study was 62 years (range 28-89); 48.3% of patients had received chemotherapy and 56.3% had received antihormonal therapy in the (neo) adjuvant setting prior to their diagnosis of advanced breast cancer, while 37.2% of patients had received no prior systemic therapy in the (neo) adjuvant setting. Most patients (97.4%) had metastatic disease at baseline; 22.7% of patients had bone only disease and 49.2% of patients had visceral disease.

The primary endpoint of the study was PFS evaluated according to RECIST version 1.1 as assessed by investigator. Secondary efficacy endpoints included objective response (OR), duration of response (DOR), clinical benefit response (CBR), overall survival (OS), safety, EQ-5D scores and health-related quality of life (QoL) assessed using the FACT-B questionnaire.

At the data cutoff date of 26 February 2016, the study met its primary objective of improving PFS. The observed HR was 0.576 (95% CI: 0.463, 0.718) in favor of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of <0.000001. An updated analysis of the primary and secondary endpoints was performed after additional 15 months of follow up (data cutoff date: 31 May 2017). A total of 405 PFS events were observed; 245 events (55.2%) in the palbociclib plus letrozole arm and 160 (72.1%) in

the comparator arm respectively.

Table 5 shows the efficacy results based on the primary and the updated analyses from the PALOMA-2 study, as assessed by the investigator and by the independent review.

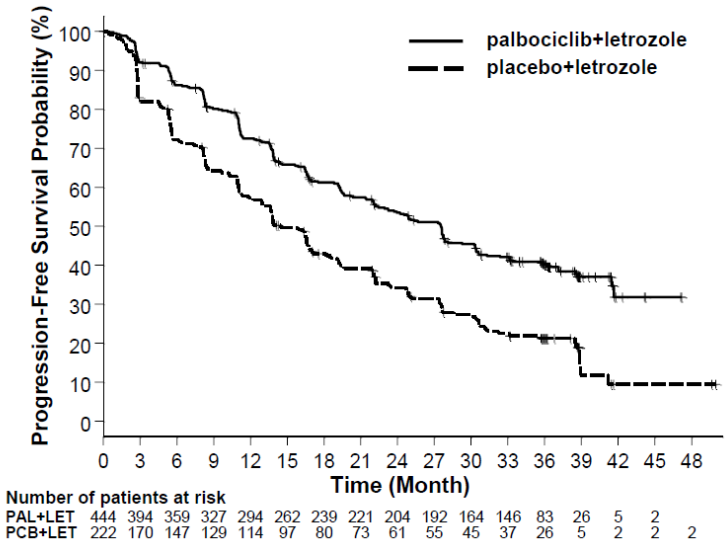
**Table 5. PALOMA-2 (Intent-to-Treat Population) - Efficacy Results Based on Primary and Updated Cutoff Dates**

| | **Primary Analysis (26 February 2016 Cutoff)** | | **Updated Analysis (31 May 2017 Cutoff)** | |
|---|---|---|---|---|
| | **Palbociclib plus Letrozole (N = 444)** | **Placebo plus Letrozole (N = 222)** | **Palbociclib plus Letrozole (N = 444)** | **Placebo plus Letrozole (N = 222)** |
| **Progression-Free Survival by Investigator Assessment** | | | | |
| Number of events (%) | 194 (43.7) | 137 (61.7) | 245 (55.2) | 160 (72.1) |
| Median PFS [months (95% CI)] | 24.8 (22.1, NE) | 14.5 (12.9, 17.1) | 27.6 (22.4 30.3) | 14.5 (12.3, 17.1) |
| Hazard ratio [(95% CI) and p-value] | 0.576 (0.463, 0.718), p<0.000001 | | 0.563 (0.461, 0.687), p<0.000001 | |
| **Progression-Free Survival by Independent Assessment** | | | | |
| Number of events (%) | 152 (34.2) | 96 (43.2) | 193 (43.5) | 118 (53.2) |
| Median PFS [months (95% CI)] and p-value | 30.5 (27.4, NE) | 19.3 (16.4, 30.6) | 35.7 (27.7, 38.9) | 19.5 (16.6, 26.6) |
| Hazard ratio (95% CI) and 1-sided p-value | 0.653 (0.505, 0.844), p=0.000532 | | 0.611 (0.485, 0.769), p=0.000012 | |
| **ORR** [% (95% CI)] | 46.4 (41.7, 51.2) | 38.3 (31.9, 45.0) | 47.5 (42.8, 52.3) | 38.7 (32.3, 45.5) |
| **ORR measurable disease** [% (95% CI)] | 60.7 (55.2, 65.9) | 49.1 (41.4, 56.9) | 62.4 (57.0, 67.6) | 49.7 (42.0, 57.4) |
| **DOR** [months (95% CI)] | 20.1 (19.3, 28.0) | 16.7 (13.8, 22.5) | 25.3 (22.1, 34.5) | 16.8 (14.2, 25.3) |
| **CBRR** [% (95% CI)] | 85.8 (82.2, 88.9) | 71.2 (64.7, 77.0) | 85.6 (82.0, 88.7) | 71.2 (64.7, 77.0) |

N=number of patients; CI=confidence interval; NE=not estimable; ORR=objective response rate; CBRR=clinical benefit response rate; DOR=duration of response; PFS=progression-free-survival. Secondary endpoints results are based on confirmed and unconfirmed responses according to RECIST 1.1.

The Kaplan-Meier curves for PFS based on the updated cutoff date of 31 May 2017 are displayed in Figure 1 below.

**Figure 1. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-2 Study (31 May 2017)**




Abbreviations: LET=letrozole; PAL=palbociclib; PCB=placebo

A series of prespecified subgroup PFS analyses was performed based on baseline demographic and disease characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in the palbociclib plus letrozole arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics in the primary and in the updated analyses.

At the time of the updated analyses, the times to initiation of the first and the second subsequent anticancer therapies were also assessed. Similarly, the time to initiation of subsequent chemotherapy was also evaluated. The results from these analyses are shown in Table 6.

**Table 6. PALOMA-2 Study: Time to Initiation of Subsequent Anticancer Therapies (31-May-2017 Cutoff Date)**

| | **Palbociclib plus letrozole (N=444)** | **Placebo plus letrozole (N=222)** |
|---|---|---|
| Median (95% CI) time to first subsequent therapy | 28.0 (23.6, 29.6) | 17.7 (14.3, 21.5) |
| Median (95% CI) time to second subsequent therapy | 38.8 (34.4, NE) | 28.8 (25.7, 33.5) |
| Median (95% CI) time to first chemotherapy | 40.4 (34.7, 47.3) | 29.9 (25.6, 35.1) |

N=number of patients; CI=confidence interval

The results of the times to initiation of the first and the second subsequent systemic anticancer therapy analyses suggest that the improvement in PFS observed with the addition of palbociclib to letrozole in the first-line treatment setting delayed the initiation of first and second subsequent anticancer therapy. Similarly, first-line palbociclib plus letrozole therapy delayed the initiation of first subsequent chemotherapy compared with placebo plus letrozole.

An analysis of time-to-deterioration composite endpoint (TTD) in Functional Assessment of Cancer Therapy-Breast (FACT-B), defined as the time between baseline and first occurrence of decrease of ≥7 points in FACT-B scores, was carried out based on survival analysis methods using a Cox proportional

hazards model and log-rank test. No statistically significant difference was observed in TTD in FACT-B total scores between the palbociclib plus letrozole arm and the placebo plus letrozole arm (HR of 1.042 [95% CI: 0.838, 1.295]; 1-sided p-value=0.663).

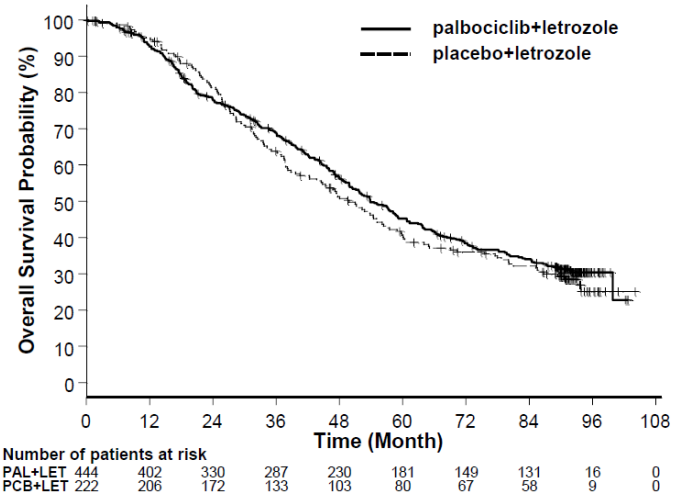
The results from the final OS analysis from the PALOMA-2 study are presented in Table 7. After a median follow-up time of 90 months, the final OS results were not statistically significant. The Kaplan-Meier plot of OS is shown in Figure 2.

**Table 7. PALOMA-2 (Intent-to-Treat Population) – Final Overall Survival Results**

| **Final Overall Survival (OS) (15 November 2021 Cutoff)** | | |
|---|---|---|
| | **Palbociclib plus letrozole (N = 444)** | **Placebo plus letrozole (N = 222)** |
| Number of OS events (%) | 287 (64.6) | 148 (66.7) |
| Number of subjects remaining in follow-up (%) | 116 (26.1) | 48 (21.6) |
| 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[†*] | |

CI=confidence interval.
[*] Not statistically significant.
[†] 1-sided p-value from the log-rank test stratified by disease site (visceral vs. non-visceral) per randomization.

**Figure 2. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-2**




*Study 3: Randomized, Phase 3 study of palbociclib in combination with fulvestrant (PALOMA-3)*

The efficacy of palbociclib in combination with fulvestrant versus placebo plus fulvestrant was evaluated in an international, randomized, double-blind, parallel-group, multicenter study conducted in women with HR-positive, HER2-negative advanced breast cancer, not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo) adjuvant or metastatic setting.

A total of 521 pre/post-menopausal women whose disease had progressed during or within 12 months after completion of adjuvant endocrine therapy or during or within 1 month after prior endocrine therapy

for advanced disease were randomized 2:1 to the palbociclib plus fulvestrant arm or the placebo plus fulvestrant arm and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus post-menopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

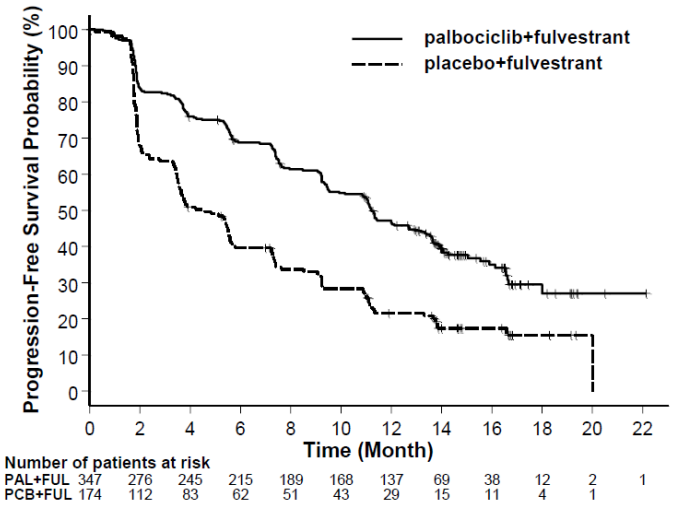
Crossover between treatment arms was not allowed.

Patients were well balanced for baseline demographics and prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. The majority of patients in each treatment arm were White, <65 years of age, had documented sensitivity to prior hormonal therapy and were post-menopausal. Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen. More than a half (62%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for the primary diagnosis.

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST version 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, DOR, CBR, OS, safety, change in QoL, and TTD. Patient-reported outcomes including Global QoL and pain were measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Breast Cancer Module (BR23) questionnaire.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events at final analysis; the results crossed the prespecified Haybittle-Peto efficacy boundary ($\alpha$=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. The estimated HR from the stratified analysis was 0.422 (95% CI: 0.318, 0.560; 1-sided $p<0.000001$) in favor of palbociclib plus fulvestrant. The mPFS was 9.2 months (95% CI: 7.5, NE) in the palbociclib plus fulvestrant arm and 3.8 months (95% CI: 3.5, 5.5) in the placebo plus fulvestrant arm.

**Figure 3. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3 (23 October 2015 Cutoff)**




CI=confidence interval; FUL=fulvestrant; N=number of patients; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

**Table 8. Tabular Summary of the Primary and Updated Analyses of Investigator-Assessed Efficacy Data Reported in Study A5481023 — Intent-to-Treat Population**

| **Efficacy Endpoint** | **Primary Analysis (Data Cutoff Date: 05 December 2014)** | | **Present Updated Analysis (Data Cutoff Date: 23 October 2015)** | |
|---|---|---|---|---|
| | **Palbociclib + Fulvestrant (N=347)** | **Placebo + Fulvestrant (N=174)** | **Palbociclib + Fulvestrant (N=347)** | **Placebo + Fulvestrant (N=174)** |
| **PFS** | | | | |
| Number of PFS events, n (%) | 102 (29.4%) | 93 (53.4%) | 200 (57.6%) | 133 (76.4%) |
| Hazard ratio (95% CI) and p-value | 0.422 (0.318, 0.560), p<0.000001 | | 0.497 (0.398, 0.620), p<0.000001 | |
| Median PFS (months [95% CI]) | 9.2 (7.5, NE) | 3.8 (3.5, 5.5) | 11.2 (9.5, 12.9) | 4.6 (3.5, 5.6) |
| | | | | |
| **OR** (% [95% CI])[a] | 10.4 (7.4, 14.1) | 6.3 (3.2, 11.0) | 21.0 (16.9, 25.7) | 8.6 (4.9, 13.8) |
| Odds ratio (95% CI) and p-value | 1.725 (0.835, 3.896), p=0.0791 | | 2.783 (1.563, 5.603), p=0.0001 | |
| **OR (measurable disease)** (% [95% CI])[a] | 13.4 (9.6, 18.1) | 8.0 (4.0, 13.8) | 27.3 (22.1, 33.1) | 10.9 (6.2, 17.3) |
| Odds ratio (95% CI) and p-value | 1.771 (0.849, 3.993), p=0.0718 | | 3.033 (1.640, 5.990), p<0.0001 | |
| | | | | |
| **CBR** (% [95% CI])[a] | 34.0 (29.0, 39.3) | 19.0 (13.4, 25.6) | 66.3 (61.0, 71.2) | 39.7 (32.3, 47.3) |
| Odds ratio (95% CI) and p-value | 2.189 (1.391, 3.523), p=0.0002 | | 3.016 (2.046, 4.565), p<0.0001 | |
| | | | | |

| | | | | |
|---|---|---|---|---|
| **DOR** (months [95% CI])[a] | 9.3 (4.0, NE) | 5.7 (3.7, 5.7) | 10.4 (8.3, NE) | 9.0 (5.6, NE) |

Data source: A5481023 CSR Tables 14.2.1.1.1, 14.2.3.1, 14.2.3.2, 14.2.5.1, and 14.2.7.1; PFS Update Report 16 March 2015 Tables 1023.407.9, 1023.407.12, 1023.407.13, 1023.407.15, and 1023.407.17; PFS Update Report 23 October 2015 Tables 1023.560.1, 1023.560.4, 1023.560.5, 1023.560.7, and 1023.560.9.
CBR=clinical benefit response; CSR=Clinical Study Report; CI=confidence interval; DOR=duration of objective response; n=number of patients meeting prespecified criteria; N=total number of patients in population; NE=not estimable; OR=objective response; PFS=progression-free survival.
a. Based on confirmed responses.

Prolongation of PFS in the palbociclib plus fulvestrant arm was also demonstrated in individual patient subgroups supporting internal consistency of PFS benefit findings within the study, and was supported by a random sample Blinded Independent Central Review (BICR) audit analysis conducted on 40.5% (N=211) of 521 randomized patients.

Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior and for duration of Study 2.

The palbociclib plus fulvestrant arm demonstrated similar clinical benefit in the pre/perimenopausal patient population (HR = 0.435 [95% CI: 0.228, 0.831]) and post-menopausal population (HR = 0.409 [95% CI: 0.298, 0.560]). Similarly, the mPFS for the palbociclib plus fulvestrant arm was 9.5 months (95% CI: 7.2, NE) in the pre/perimenopausal setting versus 9.2 months (95% CI: 7.5, NE) in the post-menopausal setting; while the mPFS in the placebo plus fulvestrant arm was 5.6 months (95% CI: 1.8, NE) in the pre/perimenopausal setting versus 3.7 months (95% CI: 3.5, 5.5) in the post-menopausal setting.

Patient-reported symptoms were assessed using the EORTC QLQ-C30 and EORTC QLQ-BR23. A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the placebo plus fulvestrant arm completed the questionnaire at baseline and at least 1 post-baseline visit.

Time to Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; $p<0.001$).

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (59.5% of randomized patients). A 6.9-month improvement in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed, although this result was not statistically significant at the prespecified significance level of 0.0235. A higher proportion of patients in the placebo plus fulvestrant arm received post-progression systemic treatments overall in comparison with the patients in the palbociclib plus fulvestrant arm (80.5% versus 71.8%) respectively. Also, in placebo plus fulvestrant arm, 15.5% of randomized patients received palbociclib and other CDK inhibitors as post-progression subsequent treatments. The results from the final OS data from PALOMA-3 Study are presented in Table 9. The relevant Kaplan-Meier plots are shown in Figures 3 and 4.

**Table 9. Efficacy Results – Study 3 (Investigator Assessment, Intent-to-Treat Population)**

| **Final Overall Survival (OS) (13 April 2018 Cutoff)** |
|---|

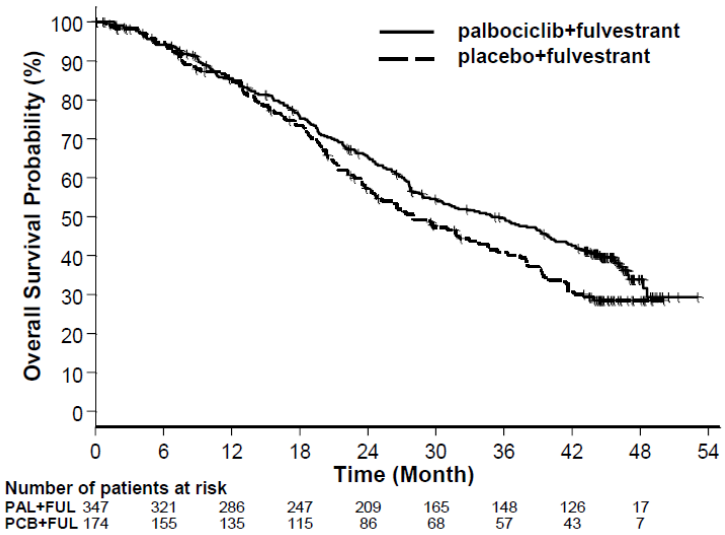
| | Palbociclib plus Fulvestrant (N=347) | Placebo plus Fulvestrant (N=174) |
|---|---|---|
| Number of events (%) | 201 (57.9) | 109 (62.6) |
| Median (months [95% CI]) | 34.9 (28.8, 40.0) | 28.0 (23.6, 34.6) |
| Hazard ratio (95% CI) and p-value† | 0.814 (0.644, 1.029) p=0.0429†* | |

CI=confidence interval.

* Not statistically significant.

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

**Figure 4. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-3**




FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

A positive treatment effect of palbociclib plus fulvestrant versus placebo plus fulvestrant on OS was observed in the majority of the prespecified subgroups. Due to the low event number and smaller sample size in some of the prespecified subgroups, the magnitude of estimated effect of palbociclib added to fulvestrant could not always be determined. The OS results from patients subgroups defined by stratification factors at randomization are reported in Table 9 below.

**Table 10. Overall Survival in Patients Subgroups Defined by Stratification Factors**

| | PAL + FUL | PCB + FUL | HR (95% CI) | p-value* |
|---|---|---|---|---|
| **ITT Sub-group** | **ne/N** | **ne/N** | | |
| **Menopausal Status at Study Entry** | | | | |
| Post-menopausal | 161/275 | 91/138 | 0.73 (0.57, 0.95) | p=0.009 |
| Peri/premenopausal | 40/72 | 18/36 | 1.07 (0.61, 1.86) | p=0.41 |
| **Documented Sensitivity to Prior Hormonal Therapy** | | | | |
| Yes | 150/274 | 84/136 | 0.72 (0.55, 0.94) | p=0.008 |
| No | 51/73 | 25/38 | 1.14 (0.70, 1.84) | p=0.297 |

| | | | | |
|---|---|---|---|---|
| **Site of Metastatic Disease** | | | | |
| Visceral | 138/206 | 72/105 | 0.85 (0.64, 1.13) | p=0.132 |
| Non-visceral | 63/141 | 37/69 | 0.69 (0.46, 1.04) | p=0.036 |

CI=confidence interval; FUL=fulvestrant; HR=Hazard Ratio; ITT=Intent-to-Treat; ne=number of events; N=number of patients; PAL=palbociclib; PCB=placebo.

* One sided p-value. No multiplicity adjustments were made for the subgroup analyses.

The estimated survival probabilities for palbociclib plus fulvestrant versus placebo plus fulvestrant were respectively: 65.3% (95% CI: 59.9, 70.2) vs. 57.3% (95% CI: 49.2, 64.6) at 2 years and 49.6% (95% CI: 44.0, 54.9) vs. 40.8% (95% CI: 32.9, 48.5) at 3 years.

## 5.2. Pharmacokinetic properties

The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

### Absorption

The time to $C_{max}$ ($T_{max}$) of palbociclib is generally between 6 to 12 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 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 1.5-4.2).

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 $AUC_{inf}$ 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 intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib should be taken with food.

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 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 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 125 mg dose of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib $AUC_{inf}$ 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 5,000 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 ($V_z/F$) was 2,583 (26%) L.

**Metabolism**

*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 sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-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 feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 25.8% of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulfotransferase (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 63.08 L/h, and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [$^{14}$C] palbociclib, a median of 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. Excretion of unchanged palbociclib in feces and urine was 2.3% and 6.9% of the administered dose, respectively.

**Age, gender, and body weight**

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging from 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.

**Elderly population**

Of 444 patients who received palbociclib in Study 2, 181 patients (41%) were ≥65 years of age. Of 347 patients who received palbociclib in Study 3, 86 patients (24.8%) were ≥65 years of age. No overall differences in safety or effectiveness of palbociclib were observed between these patients and younger patients.

**Hepatic impairment**

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound $AUC_{inf}$) 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 hepatic impairment (Child-Pugh class C), 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 (PK) of palbociclib.

**Renal impairment**

Data from a pharmacokinetic trial in subjects with varying degrees of renal function indicate that total palbociclib exposure ($AUC_{inf}$) was 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 PK of palbociclib. The pharmacokinetics of palbociclib has not been studied in patients requiring hemodialysis.

**Asian race**

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.

**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 did not prolong QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

**5.3. Preclinical safety data**

The primary target organ findings following single and/or repeat dosing included hematolymphopoietic and male reproductive organ effects in rats and dogs, and effects on bone and actively growing incisors in rats only. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. Partial to full reversal of effects on the hematolymphopoietic, male reproductive systems, and incisor teeth were established, whereas the bone effect was not reversed following a 12-week nondosing period. In addition, cardiovascular effects (QTc prolongation, decreased heart rate, and increased RR

interval and systolic blood pressure) were identified in telemetered dogs at ≥4 times human clinical exposure based on $C_{max}$.

**Carcinogenicity**

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell tumors in the central nervous system of males at 30 mg/kg/day; there were no neoplastic findings in female rats at any dose up to 200 mg/kg/day. The NOEL for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times the human clinical exposure based on AUC) and 200 mg/kg/day (approximately 4 times the human clinical exposure based on AUC) in males and females, respectively. The relevance of the male rat neoplastic finding to humans is unknown.

**Genotoxicity**

Palbociclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the *in vitro* human lymphocyte chromosome aberration assay.

Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells *in vitro* and in the bone marrow of male rats at doses ≥100 mg/kg/day. The no-observed effect level for aneugenicity was approximately 7 times human clinical exposure based on AUC.

**Impairment of fertility**

Palbociclib did not affect mating or fertility in female rats at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC) and no adverse effects were observed in female reproductive tissues in repeat-dose toxicity studies up to 300 mg/kg/day in the rat and 3 mg/kg/day in the dog (approximately 5 and 3 times human clinical exposure based on AUC, respectively).

Palbociclib is considered to have the potential to impair reproductive function and fertility in male humans based on nonclinical findings in rats and dogs. Palbociclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, and decreased secretion. These findings were observed in rats and/or dogs at exposures ≥9 times or subtherapeutic compared to human clinical exposure based on AUC. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week non-dosing period, respectively. Despite these male reproductive organ findings, there were no effects on mating or fertility in male rats at projected exposure levels 13 times human clinical exposure based on AUC.

**Developmental toxicity**

Palbociclib was fetotoxic in pregnant animals. An increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra) at ≥100 mg/kg/day was observed in rats. Reduced fetal body weights were observed at a maternally toxic dose of 300 mg/kg/day in rats (3 times human clinical exposure based on AUC), and an increased incidence of skeletal variations, including small phalanges in the forelimb was observed at a maternally toxic dose of 20 mg/kg/day in rabbits (4

times human clinical exposure based on AUC). Actual fetal exposure and cross-placenta transfer have not been examined.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Capsule content
Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate

Capsule shell
Gelatin
Red iron oxide – for 100mg and 125mg shell only
Titanium dioxide

Printing ink
Shell-lac
Dehydrated Alcohol
Isopropyl Alcohol
Butyl Alcohol
Propylene Glycol
Strong Ammonia Solution
Black Iron Oxide
Potassium Hydroxide
Purified Water

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf-life

Please refer to outer carton.

### 6.4. Special precautions for storage

Do not store above 30°C.

### 6.5. Nature and contents of container

Plain clear PVC/Aclar and L/F plain Aluminium hard foil blisters containing 7 and 21 capsules.

*Not all pack size may be marketed.*

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

No special requirements.

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

## 7. MANUFACTURER

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## 8. DATE OF REVISION OF THE TEXT

Jan 2024