PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTARO-PALBOCICLIB

Palbociclib

Tablets, 75 mg, 100 mg and 125 mg, oral

Protein Kinase Inhibitor

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	01/2025
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TARO-PALBOCICLIB (palbociclib tablets) is indicated for:

the treatment of pre/perimenopausal or postmenopausal women, or men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with:

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

Pre/perimenopausal women and men treated with the combination TARO-PALBOCICLIB plus aromatase inhibitor therapy, and pre/perimenopausal women treated with the combination TARO-PALBOCICLIB plus fulvestrant therapy should also be treated with a luteinizing hormone releasing hormone (LHRH) agonist.

Clinical effectiveness of TARO-PALBOCICLIB in combination with an aromatase inhibitor is based on the benefit observed in patients treated with palbociclib in combination with letrozole for the treatment of postmenopausal women with advanced breast cancer.

1.1 Pediatrics

Pediatrics (<18 years of age):

Based on the limited data submitted and reviewed by Health Canada, the safety and efficacy of palbociclib in pediatric patients have not been established; Therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics and 10.3 Pharmacokinetics, Special Populations and Conditions).

1.2 Geriatrics

Geriatrics (≥65 years of age): Of 444 patients who received palbociclib in PALOMA-2, 181 (41%) patients were ≥65 years of age. Of 347 patients who received palbociclib plus fulvestrant, 86 patients (25%) were ≥65 years of age. No overall differences in the safety and efficacy of palbociclib were observed between these patients and younger patients in either study. Anemia was reported more frequently in patients ≥65 than in patients <65 years of age treated with palbociclib plus letrozole, whereas similar incidences were reported in both age groups for patients treated with palbociclib plus fulvestrant (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
TARO-PALBOCICLIB should be prescribed and managed by a qualified physician who is experienced in the use of anti-cancer agents. The following is a significant adverse drug reaction identified in clinical trials conducted with palbociclib: • Neutropenia (see 7 WARNINGS AND PRECAUTIONS, Hematologic)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Pre/perimenopausal women and men treated with the combination IBRANCE plus aromatase inhibitor therapy, and pre/perimenopausal women treated with the combination IBRANCE plus fulvestrant therapy should also be treated with LHRH agonists according to local clinical practice.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of TARO-PALBOCICLIB (palbociclib) is a 125 mg tablet taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

TARO-PALBOCICLIB is used in combination with an aromatase inhibitor or fulvestrant. For full dosing instructions of the selected aromatase inhibitor or fulvestrant, please consult the corresponding Product Monographs.

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

Table 1. TARO-PALBOCICLIB Recommended Dose Modification for Adverse Events

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 palbociclib treatment.

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

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

Grading according to CTCAE 4.0

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] Absolute neutrophil count (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. TARO-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: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next reduced dose level.

Grading according to CTCAE 4.0
CTCAE=Common Terminology Criteria for Adverse Events.

No dose adjustments are required on the basis of age, gender, or body weight (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Permanently discontinue TARO-PALBOCICLIB in patients with severe interstitial lung disease (ILD) or pneumonitis (see 7 WARNINGS AND PRECAUTIONS, Respiratory).

Special populations
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 TARO-PALBOCICLIB is 75 mg once daily on Schedule 3/1 (see 10.3 Pharmacokinetics).

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥15 mL/min). There are no data available in patients requiring hemodialysis (see 10.3 Pharmacokinetics).

4.4 Administration
TARO-PALBOCICLIB tablets may be taken with or without food.

Patients should be advised 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.

4.5 Missed Dose
If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. TARO-PALBOCICLIB tablets should be swallowed whole (do not chew, crush or split the tablets prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

5 OVERDOSAGE
There is no known antidote for TARO-PALBOCICLIB (palbociclib). The treatment of overdose of TARO-PALBOCICLIB should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets / 75 mg, 100 mg, 125 mg	Anhydrous citric acid, colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, sodium stearyl fumarate, succinic acid. Film coating material: 75 mg and 125 mg tablets: FD&C blue #2, hypromellose, iron oxide red, titanium dioxide, and triacetin. 100 mg tablets: FD&C blue #2, hypromellose, iron oxide yellow, titanium dioxide, and triacetin.

TARO-PALBOCICLIB is supplied in the following strengths and package configurations:

TARO-PALBOCICLIB Tablets		
Package Configuration	**Tablet Strength (mg)**	**Dosage Form Description**
Box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	125	Oval, light purple, film-coated tablets debossed with "**S28**" on one side and plain on the other side.
Box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	100	Oval, Green, film-coated tablets debossed with "**S27**" on one side and plain on the other side.
Box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	75	Round, light purple, film-coated tablets debossed with "**S26**" on one side and plain on the other side.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.**

General

Drug-Drug Interactions

CYP3A inhibitors: Concomitant use of TARO-PALBOCICLIB and CYP3A inhibitors (e.g. clarithromycin, itraconazole, ritonavir, ketoconazole, grapefruit or grapefruit juice) may increase exposure to palbociclib. In patients receiving TARO-PALBOCICLIB, coadministration of a strong CYP3A inhibitor should be avoided (see 9 DRUG INTERACTIONS).

CYP3A substrates: Concomitant use of TARO-PALBOCICLIB and a CYP3A substrate may increase exposure to the CYP3A substrate. Caution is warranted when TARO-PALBOCICLIB is co-administered with CYP3A substrates of narrow therapeutic index, such as alfentanil, cyclosporine, dihydroergotamine, or ergotamine (see 9 DRUG INTERACTIONS).

CYP3A inducers: Concomitant use of TARO-PALBOCICLIB and CYP3A inducers (e.g. strong inducers such as rifampin, carbamazepine, phenytoin, St John's Wort, and moderate inducers such as nafcillin, bosentan, modafinil) may decrease palbociclib plasma concentration. In patients receiving TARO-PALBOCICLIB coadministration of strong CYP3A inducers should be avoided (see 9 DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

An increased incidence of palbociclib-related microglial cell tumors was observed in the central nervous system of male rats; there were no neoplastic findings in female rats or in mice. The No Observed Effect Level [NOEL] for palbociclib-related carcinogenicity effects in rats was approximately 2-4 times the human clinical exposure based on AUC. The relevance of the male rat neoplastic finding to humans is unknown (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity).

Cardiovascular

Cardiac Electrophysiology

The effect of palbociclib in combination with letrozole on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline in 77 patients with breast cancer from an ECG substudy of PALOMA-2. This study suggested that palbociclib at 125 mg once daily (Schedule 3/1), when added to letrozole, had no large effect on QTc (i.e., >20 msec) (see 10 CLINICAL PHARMACOLOGY).

Venous Thromboembolism

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), venous thromboembolic events (VTEs) were reported in 3.4% of patients treated with palbociclib plus an endocrine therapy (n=872), compared with 1.9% of patients treated with the endocrine therapy alone (n=471). Venous thromboembolic events included pulmonary embolism, embolism, deep vein thrombosis, peripheral embolism, and thrombosis. Monitor patients for signs and symptoms of VTEs and treat as medically appropriate.

Driving and Operating Machinery

No studies of the effects of palbociclib on the ability to drive or operate machinery have been conducted. However, since fatigue and dizziness have been reported with the use of palbociclib, patients should exercise caution when driving or operating machinery while taking TARO-PALBOCICLIB.

Hematologic

Neutropenia

Neutropenia was the most frequently reported adverse reaction in patients treated with palbociclib plus letrozole (80%) or palbociclib plus fulvestrant (83%). Grade 3 decreased neutrophil counts were observed in approximately half of all patients, and Grade 4 decreased neutrophil counts were observed in 5% and 11% of patients treated with palbociclib in combination with letrozole or fulvestrant, respectively (see 8 ADVERSE REACTIONS).

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

Febrile neutropenia has been reported in 1.8% of patients across the palbociclib clinical trials. One patient treated with palbociclib plus fulvestrant died due to neutropenic sepsis. Physicians should inform patients to promptly report any episodes of fever.

Monitor complete blood count prior to the start of TARO-PALBOCICLIB therapy, at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia (see 4.2 Recommended Dose and Dosage Adjustment). For patients who experience Grade 3 neutropenia, consider repeating complete blood count monitoring one week later.

Other Hematologic Parameters

Decreases in leukocytes and platelets were observed in patients treated with either palbociclib plus letrozole or palbociclib plus fulvestrant. Grade 3 leukopenia was reported in 24% of palbociclib plus letrozole patients and in 30% of palbociclib plus fulvestrant patients. Decreased hemoglobin and lymphocytes were also observed in palbociclib plus letrozole-treated patients (see 8 ADVERSE REACTIONS).

In clinical trials with palbociclib, anemia and leukopenia were usually managed with temporary palbociclib discontinuation and/or dose reduction. Monitor complete blood count prior to the start of TARO-PALBOCICLIB therapy, at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 4.2 Recommended Dose and Dosage Adjustment).

Hepatic/Biliary/Pancreatic

Hepatic Impairment: The pharmacokinetics of palbociclib has been studied in subjects with hepatic impairment. No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). The recommended dose of TARO-PALBOCICLIB for patients with severe hepatic impairment (Child-Pugh class C) is 75 mg once daily on Schedule 3/1 (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics). There are no efficacy and safety data available for palbociclib in breast cancer patients with hepatic impairment. Monitor patients for signs of toxicity.

Immune

Infections

TARO-PALBOCICLIB may predispose patients to infections. Infections have been more frequently reported in patients treated with palbociclib plus letrozole (60%) and in patients treated with palbociclib plus fulvestrant (47%) than those treated in the respective comparator arms (42% and 31%, respectively). Grade ≥3 infections occurred in 6% of patients treated with palbociclib plus letrozole and in 3% of patients treated with letrozole alone. Grade ≥3 infections occurred in 3% of patients treated with either palbociclib plus fulvestrant or placebo plus fulvestrant. Monitor patients for signs and symptoms of infection and treat as medically appropriate (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Physicians should be aware of the increased risk of infection with TARO-PALBOCICLIB and should inform patients to promptly report any episodes of fever.

Monitoring and Laboratory Tests

Patients treated with TARO-PALBOCICLIB should be monitored for signs and symptoms of myelosuppression and infection. Dose modification may be required (see 4.2 Recommended Dose and Dosage Adjustment).

Monitor complete blood count prior to starting TARO-PALBOCICLIB therapy and at the beginning of each cycle, as well as on Day 15 of the first two cycles, and as clinically indicated.

For patients who experience Grade 3 neutropenia, consider repeating complete blood count monitoring one week later. For patients who develop Grade 3 or 4 neutropenia, refer to the dose modification tables (see 4.2 Recommended Dose and Dosage Adjustment).

Renal

Renal Impairment: The pharmacokinetics of palbociclib has been studied in subjects with renal impairment. No dose adjustments are required for patients with mild, moderate, or severe renal impairment. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics)**.** There are no efficacy and safety data available for palbociclib in breast cancer patients with renal impairment.

Reproductive Health: Female and Male Potential

- **Fertility**

No clinical data have been obtained on fertility in humans. There were no effects on estrous cycle or mating and fertility in female rats in nonclinical studies (see 10.3 Pharmacokinetics, Special Populations and Conditions). Based on nonclinical safety findings in male reproductive tissues, male fertility may be impaired by treatment with TARO-PALBOCICLIB (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Men should consider sperm preservation prior to beginning therapy with TARO-PALBOCICLIB. Because of the potential for genotoxicity, male patients with female partners of childbearing potential should use adequate contraceptive methods during therapy and for at least 97 days after completing therapy.

Respiratory

Interstitial lung disease/pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with TARO-PALBOCICLIB when taken in combination with endocrine therapy.

Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3, n = 872), 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 8.5 Post-Market Adverse Reactions), with fatalities reported.

Patients should be monitored 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 TARO-PALBOCICLIB immediately and evaluate the patient. TARO-PALBOCICLIB should be permanently discontinued in patients diagnosed with severe drug-related ILD/pneumonitis (see 4.2 Recommended Dose and Dosage Adjustment).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies using palbociclib in pregnant women.

TARO-PALBOCICLIB may cause fetal harm when administered to a pregnant woman. In animal studies, palbociclib was shown to be fetotoxic in pregnant rats and rabbits (see 16 NON-CLINICAL TOXICOLOGY).

TARO-PALBOCICLIB should not be used during pregnancy. If TARO-PALBOCICLIB is used in women of childbearing potential, advise the patient to avoid becoming pregnant with the use of adequate contraceptive methods during therapy and for at least 21 days after completing therapy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

7.1.2 Breast-feeding

It is not known whether palbociclib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TARO-PALBOCICLIB, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the patient.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the limited data submitted and reviewed by Health Canada, the safety and efficacy of palbociclib in pediatric patients have not been established; Therefore, Health Canada has not authorized an indication for pediatric use.

In a Phase 1 pediatric study the safety was evaluated in 34 patients (≥4 years and ≤21 years of age) including 30 pediatric patients (≥4 years and <18 years of age) with progressive or refractory brain tumors (except low grade gliomas) with intact Rb protein. The maximum

tolerated dose was determined to be 75 mg/m^2 administered orally once daily for 21 days of a 28-day cycle. Similar to the side effect profile in adults, the most common adverse events were related to myelosuppression with decrease in white blood cells, neutrophils, lymphocytes, and platelets being the most common. The overall safety profile was consistent with that reported from palbociclib use in adults and the diseases under study.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Population pharmacokinetic analysis was performed on data from 183 patients with cancer in an age range from 22 to 89 years. There was no clinically important difference in palbociclib exposure in patients ≥65 years of age compared with patients <65 years of age. In palbociclib plus letrozole-treated patients, anemia was reported more frequently in patients ≥65 years of age than in those <65 years of age, whereas similar incidences were reported in both age groups in patients treated with palbociclib plus fulvestrant.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of palbociclib has been assessed in 2 randomized studies of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The most common adverse drug reactions of any grade reported in ≥10% of patients receiving palbociclib in combination with endocrine treatment were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, thrombocytopenia, diarrhea, alopecia, vomiting, decreased appetite, and rash.

Most patients treated with palbociclib experienced myelosuppressive effects with over half experiencing Grade 3 neutropenia at some point during treatment. Thrombocytopenia and anemia were less commonly observed. Myelosuppressive effects can be expected to occur from Cycle 1 forward.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Palbociclib plus Letrozole for the initial endocrine -based therapy of patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer (PALOMA-2)

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 palbociclib plus letrozole in PALOMA-2. Patients were randomized 2:1 to receive the combination palbociclib plus letrozole versus placebo plus letrozole. 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 treatment discontinuation associated with an adverse reaction occurred in 43 of 444 (10%) patients receiving palbociclib plus letrozole and in 13 of 222 (6%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving palbociclib plus letrozole included neutropenia (1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions (≥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 serious adverse reactions (≥1%) in patients receiving palbociclib plus letrozole were Infections (20%) and Febrile neutropenia (2%).

Adverse reactions (≥5%) reported in patients who received palbociclib plus letrozole or placebo plus letrozole in PALOMA-2 are listed in Table 5.

Table 5. Adverse Reactions Reported (With a Frequency of ≥5% on the Palbociclib plus letrozole arm) in PALOMA-2

	Palbociclib plus Letrozole (N=444)			**Placebo plus Letrozole (N=222)**		
Adverse Reaction	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Blood and lymphatic system disorders						
Neutropenia[a]	80	56	10	6	1	1
Leukopenia[b]	39	24	1	2	0	0
Anemia[c]	24	5	<1	9	2	0
Thrombocytopenia[d]	16	1	<1	1	0	0
Eye Disorders						
lacrimation increased	6	0	0	1	0	0
Gastrointestinal disorders						
Stomatitis[e]	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0

	Palbociclib plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
Adverse Reaction	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Vomiting	16	1	0	17	1	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
Infections and infestations						
Infections[f,g]	60	6	1	42	3	0
Investigations						
Alanine aminotransferase increased	10	2	<1	4	0	0
Aspartate aminotransferase increased	10	3	0	5	1	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	9	0	0	6	0	0
Skin and subcutaneous tissue disorders						
Alopecia	33	N/A	N/A	16	N/A	N/A
Rash[h]	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0

Grading according to CTCAE4.0.

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

[a] Neutropenia includes: Neutropenia and Neutrophil count decreased

[b] Leukopenia includes: Leukopenia and White blood cell count decreased

[c] Anemia includes: Anaemia, Haematocrit decreased and Haemoglobin decreased

[d] Thrombocytopenia includes: Platelet count decreased and Thrombocytopenia

[e] Stomatitis includes: aphthous ulcer, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.

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

[g] Most common infections (>1%) are: 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.

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

Palbociclib plus fulvestrant for the treatment of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy (PALOMA-3)

The safety of palbociclib (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in a randomized, controlled, Phase 3 trial (PALOMA-3). The data described below reflect exposure to palbociclib in 345 out of 517 patients with HR-positive, HER2- negative metastatic breast cancer who received at least 1 dose of palbociclib in PALOMA-3. Patients were randomized 2:1 to receive the combination palbociclib plus fulvestrant versus placebo plus fulvestrant.

The most common adverse reactions (≥10%) of any grade reported in patients in the palbociclib plus fulvestrant arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported serious adverse reactions in patients receiving palbociclib plus fulvestrant were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%).

Adverse reactions reported in patients who received palbociclib plus fulvestrant or placebo plus fulvestrant in PALOMA-3 are listed in Table 6.

Discontinuation and dose reduction due to AEs

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 permanent discontinuation for those patients receiving palbociclib plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

Treatment-emergent adverse events presented in Table 6 below are based on a median duration of treatment of approximately 5 months for patients on the palbociclib plus fulvestrant arm, and approximately 4 months for patients on the placebo plus fulvestrant arm.

Table 6. Adverse Events* Reported (With a Frequency of ≥5% on the Palbociclib Arm) for Patients Who Received Palbociclib Plus Fulvestrant or Placebo Plus Fulvestrant in PALOMA-3

Adverse Reaction	Palbociclib plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders						

Adverse Reaction	Palbociclib plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Neutropenia[a]	79	53	9	4	0	<1
Leukopenia[b]	46	25	<1	4	0	1
Anemia[c]	26	3	0	10	2	0
Thrombocytopenia[d]	19	2	<1	0	0	0
Gastrointestinal disorders						
Nausea	29	0	0	26	<1	0
Stomatitis[e]	25	<1	0	11	0	0
Diarrhea	19	0	0	17	<1	0
Constipation	17	0	0	14	0	0
Vomiting	15	<1	0	12	<1	0
Abdominal Pain	6	<1	0	5	0	0
General disorders and administration site conditions						
Fatigue	38	2	0	27	1	0
Asthenia	7	0	0	5	1	0
Pyrexia	9	<1	0	4	0	0
Oedema peripheral	8	0	0	5	0	0
Infections and infestations						
Infections[f]	34	1	<1	24	2	0
Metabolism and nutrition disorders						
Decreased appetite	13	<1	0	8	0	0
Nervous system disorders						
Headache	21	<1	0	17	0	0
Dysgeusia	6	0	0	2	0	0
Dizziness	11	<1	0	9	0	0
Psychiatric disorders						
Insomnia	11	<1	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	6	0	0	1	0	0
Cough	13	0	0	11	0	0
Dyspnoea	7	0	0	4	0	0
Skin and subcutaneous tissue disorders						
Alopecia	15	N/A	N/A	6	N/A	N/A
Rash[g]	14	<1	0	5	0	0
SOC Investigations						
Aspartate aminotransferase increased	6	2	0	5	1	0

*Adverse events reported with a frequency of ≥5% on the palbociclib arm and a higher frequency on the palbociclib arm compared to the placebo arm Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.

[a] Neutropenia includes: neutropenia and neutrophil count decreased

[b] Leukopenia includes: leukopenia and white blood cell count decreased

[c] Anemia includes: anaemia, haemoglobin decreased, and hematocrit decreased

[d] Thrombocytopenia includes: thrombocytopenia and platelet count decreased

[e] Stomatitis includes: aphthous ulcer, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

[f] Infections includes any reported PTs that are part of the System Organ Class Infections and infestations.

[g] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

8.3 Less Common Clinical Trial Adverse Reactions

Palbociclib plus Letrozole for the initial endocrine-based therapy of patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer (PALOMA-2)

Additional adverse reactions occurring at an overall incidence of <5% of patients receiving palbociclib plus letrozole in PALOMA-2 included:
Blood and lymphatic system disorders- febrile neutropenia (2.5%)
Cardiovascular - venous thromboembolism* (3.4%)
Ophthalmologic-dry eye (4.1%), vision blurred (3.6%),

Palbociclib plus fulvestrant for the treatment of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy (PALOMA-3)

Additional adverse reactions occurring at an overall incidence of <5% of patients receiving palbociclib plus fulvestrant in Study PALOMA-3 included:
Blood and lymphatic system disorders – febrile neutropenia (0.6%)
Cardiovascular - venous thromboembolism* (2.3%)
Investigations - alanine aminotransferase increased (4.6%)
Ophthalmologic - Vision blurred (4.9%), lacrimation increased (4.3%), dry eye (2.9%)
Skin -dry skin (4.9%)

*Venous thromboembolism includes pulmonary embolism, embolism, deep vein thrombosis, peripheral embolism, and thrombosis.

8.4 Abnormal Hematologic and Clinical Chemistry Findings

Palbociclib plus Letrozole for the initial endocrine-based therapy of patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer (PALOMA-2)

Table 7. Laboratory Test Abnormalities in PALOMA-2

	Palbociclib plus Letrozole (N=444)			Placebo plus Letrozole (N=222)		
Laboratory Test Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**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

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

Palbociclib plus fulvestrant for the treatment of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy (PALOMA-3)

Table 8. Incidence of Hematology Laboratory Abnormality for Patients Who Received Palbociclib Plus Fulvestrant or Placebo Plus Fulvestrant in PALOMA -3

Laboratory Abnormality	**Palbociclib + Fulvestrant (N=345)**			**Placebo Plus Fulvestrant (N=172)**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
White blood cells decreased	98	40	1	22	0	<1
Neutrophils decreased	95	53	9	11	0	1
Anemia	76	3	0	36	2	0
Platelets decreased	57	2	1	8	0	0

N=number of subjects.

Updated safety data for patients on the palbociclib plus fulvestrant arm, based on an approximate 6-month increase in the median duration of treatment, were generally consistent with the safety table provided in Tables 6 and 8. No new safety concerns have been identified.

8.5 Post-Market Adverse Reactions

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, including fatal cases.

Skin and subcutaneous tissue disorders: Palmar-plantar erythrodysesthesia syndrome.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Palbociclib is a substrate and weak inhibitor of CYP3A. It is also a moderate substrate of P - glycoprotein (P-gp) in vitro. Drug interactions were observed when palbociclib was coadministered with a strong CYP3A inhibitor and a strong CYP3A inducer. The aqueous solubility of palbociclib is pH-dependent. Coadministration of palbociclib tablets with PPIs under fasted conditions had no effect on palbociclib absorption. *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.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 9 - Established or Potential Drug-Drug Interactions

Non-proprietary name(s) of the drug product(s)	Source of Evidence	Effect	Clinical comment
Agents that may increase palbociclib concentrations			
Strong CYP3A inhibitors including but not limited to Itraconazole, clarithromycin, indinavir, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin,	CT	Data from a drug-drug interaction study indicated that palbociclib AUC_{inf} and C_{max} increased by approximately 87% and 34%, respectively following coadministration of multiple 200 mg daily doses of itraconazole with a single 125 mg palbociclib dose	The concomitant use of strong CYP3A inhibitors should be avoided.

Non-proprietary name(s) of the drug product(s)	Source of Evidence	Effect	Clinical comment
voriconazole, and grapefruit or grapefruit juice			
Agents that may decrease palbociclib concentration			
Strong CYP3A inducers including but not limited to rifampin, carbamazepine, enzalutamide, phenytoin, St. John's wort	CT	Data from a drug-drug interaction study indicated that coadministration of multiple 600 mg doses of rifampin with a single 125 mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by approximately 85% and 70%, respectively	The concomitant use of strong CYP3A inducers should be avoided.
Moderate CYP3A inducers including but not limited to modafinil, bosentan, efavirenz, etravirine, modafinil, and nafcillin	CT	Data from a drug interaction study indicated that coadministration of multiple 400 mg daily doses of modafinil, with a single 125 mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by approximately 32% and 11%, respectively	If concomitant use of palbociclib with moderate CYP3A inducers cannot be avoided, no dosing adjustments are required for palbociclib.
Agents that may have their plasma concentrations altered by palbociclib			
Sensitive CYP3A substrates with a narrow therapeutic index, including but not limited to midazolam, alfentanil, cyclosporine, dihydroergotamine,	CT	Coadministration of midazolam with multiple doses of palbociclib increased midazolam AUC_{inf} and the C_{max} values by 61% and 37% respectively	The dose of the sensitive CYP3A substrate with a narrow therapeutic index) may need to be reduced.

Non-proprietary name(s) of the drug product(s)	Source of Evidence	Effect	Clinical comment
ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus			

Legend: CT = Clinical Trial

Gastric pH Elevating Medications:

Tablets: Data from a study in healthy subjects indicated that coadministration of a single 125 mg palbociclib tablet with multiple doses of the PPI rabeprazole under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg palbociclib tablet administered alone. The effect of coadministration of a single 125 mg palbociclib tablet with multiple doses of the PPI rabeprazole under fed conditions have not been evaluated in clinical studies.

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 is expected to be minimal.

Luteinizing Hormone Releasing Hormone (LHRH) Agonists

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 coadministered. Drug-drug interaction studies between palbociclib and other LHRH agonists have not been performed.

In vitro studies with transporters

In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 at clinically relevant concentrations.

In vitro studies demonstrate that palbociclib is not a substrate of OATP1B1 or OATP1B3.

9.5 Drug-Food Interactions

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase palbociclib plasma concentrations and should be avoided.

Tablets: The effect of food on palbociclib exposure following administration of palbociclib tablets was evaluated in healthy subjects. Compared to palbociclib tablets given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 22% and 26%, respectively, when palbociclib tablets were given with a high-fat, high-calorie meal, and by 9% and 10%, respectively, when palbociclib tablets were given with a moderate-fat, standard-calorie meal. Food intake had no significant impact on the variability of palbociclib exposure following administration with palbociclib tablets. Based on these results, TARO-PALBOCICLIB

tablets may be taken with or without food.

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4/5 that may decrease palbociclib plasma concentrations and should be avoided.

9.7 Drug-Laboratory Test Interactions
Interactions between TARO-PALBOCICLIB and laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Palbociclib is a selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. Through inhibition of cyclin D-CDK4/6 complex activity, palbociclib inhibits the phosphorylation of retinoblastoma (Rb) protein, blocking cell cycle progression from G1 into S phase. In a panel of molecularly profiled breast cancer cell lines, palbociclib exhibited the greatest efficacy towards the luminal ER-positive subtype; particularly, in cell lines with increased Rb and cyclin D1 and decreased p16 gene expression. In combination with anti-estrogen agents, palbociclib demonstrated enhanced inhibition of cell proliferation and induction of cell senescence in ER-positive breast cancer models.

10.2 Pharmacodynamics

Cardiac Electrophysiology
The effect of palbociclib in combination with letrozole on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline at 5 timepoints during the dosing interval at steady-state in 77 patients with breast cancer. The exposure/response analysis showed a slight positive linear relationship between QTcF and palbociclib concentration, with a mean QTcF increase of 4.14 msec at the mean steady-state palbociclib C_{max}, and an upper bound of the 1-sided 95% CI <7 msec. No patients had a post-baseline absolute mean maximum QTcF ≥480 msec or an increase from QTcF time - matched baseline value ≥60 msec during the QTc assessment period. The proportions of patients with observed changes from baseline in QTc parameters between 30 and 60 msec were comparable between the palbociclib plus letrozole and placebo plus letrozole arms. These data suggested that palbociclib, at the recommended dosing regimen of 125 mg daily, when added to letrozole, had no large effect on QTc (>20 msec).

10.3 Pharmacokinetics
The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects. Pharmacokinetic parameters of palbociclib and letrozole obtained from study A5481003 are shown in Table 10.

Table 10 Summary of Plasma Pharmacokinetic Parameters of Palbociclib (125 mg QD) and Letrozole (2.5 mg QD) at Steady State When Administered Alone or in Combination to Patients with Advanced Breast Cancer in the Phase 1 Portion of A5481003

Palbociclib PK Parameter Summary Statistics[a]						
Treatment	**C_{max} (ng/mL)**	**$AUC_{(0-24)}$ (ng.hr/mL)**	**T_{max} (hr)**	**$t_{½}$ (hr)**	**CL/F (L/hr)**	**V_zF (L)**
PLB alone (N=12)	116 (28)	1982 (29)	7.9 (2.2-8.2)	28.8 (±5.0)	63.1 (29)	2583 (26)
PLB + LTZ (N=12)	108 (29)	1933 (31)	7.9 (2.0-8.1)	-	-	-
Letrozole PK Parameter Summary Statistics[a]						
LTZ alone (N=12)	104 (31)	1936 (35)	1.0 (0-4.4)	-	-	-
LTZ + PLB (N=12)	95.0 (27)	1739 (30)	2.0 (0.8-4.1)	-	-	-

$AUC_{(0-24)}$ =area under the plasma concentration-time curve from time 0 to 24 hours after dosing; CL/F=apparent oral clearance; C_{max}=maximum observed plasma concentration; CSR=Clinical Study Report;
%CV=percent coefficient of variation; LTZ=letrozole; N=total number of patients in the treatment arm;
PK=pharmacokinetic; PLB=Palbociclib; QD=once daily; Std Dev=standard deviation; T_{max}= time to first occurrence of C_{max};
$t_{1/2}$=terminal plasma half-life; V_z/F=apparent volume of distribution.
a. Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for T_{max} and arithmetic mean (±Std Dev) for $t_{1/2}$.

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

Food effect:
Tablets: The effect of food on palbociclib exposure following administration of palbociclib tablets was evaluated in healthy subjects. Compared to palbociclib tablets given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 22% and 26%, respectively, when palbociclib tablets were given with a high-fat, high-calorie meal, and by 9% and 10%, respectively, when palbociclib tablets were given with a moderate-fat, standard-calorie meal.

Food intake had no significant impact on the variability of palbociclib exposure following administration with palbociclib tablets. Based on these results, palbociclib tablets may be taken with or without food.

Distribution: Binding of palbociclib to human plasma proteins *in vitro* was ~85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The mean fraction of unbound (f_u) palbociclib in human plasma *in vivo* increased 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.

Metabolism: In vitro and in vivo studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [^{14}C] palbociclib to humans, the 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 (23% of total radioactivity in plasma). The major circulating metabolite was a glucuronide conjugate of palbociclib (14.8% of total radioactivity in plasma), although it only represented 1.5% of the administered dose in the excreta. 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/hr, 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. The majority of the material was excreted as metabolites. Excretion of unchanged palbociclib in feces and urine was 2.3% and 6.9% of the administered dose, respectively.

Special Populations and Conditions:

Age, Gender, and Body Weight
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), sex had no effect on the exposure of palbociclib, and neither age nor body weight had a clinically important effect on the exposure of palbociclib.

Pediatric (< 18 years of age): Based on the limited data submitted and reviewed by Health Canada, the safety and efficacy of palbociclib in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

In a Phase 1 pediatric study in 34 patients (≥4 years and ≤21 years of age) including 30 pediatric patients (≥4 years and < 18 years of age) with progressive or refractory brain tumors (except low grade gliomas) with intact Rb protein, palbociclib was administered orally as a single agent at 50, 75, and 95 mg/m^2 dose levels daily for the first 21 days of a 28-day cycle. The maximum tolerated dose was determined to be 75 mg/m^2 daily for 21 days of a 28-day cycle. Following single and repeated doses, mean palbociclib C_{max} and AUC_{last} in the pediatric patients increased in approximately dose proportional manner. Palbociclib was absorbed with a median T_{max} of 4 to 8 hours across the 50, 75, and 95 mg/m^2 dose levels. The mean palbociclib C_{max} and AUC_{24} at steady-state at the 75 mg/m^2 dose level in the pediatric patients were 109 ng/mL and 1706 ng•hr/mL, respectively. The observed palbociclib steady-state exposure (C_{max} and AUC_{24}) at the 75 mg/m^2 dose level in this study were similar to that observed in adult patients following daily 125 mg palbociclib doses.

Hepatic Impairment
A pharmacokinetic trial was conducted in subjects with varying degrees of hepatic function who were administered a single 75 mg dose of palbociclib. In this study, palbociclib unbound exposure (unbound AUC_{inf}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer where 40 patients had mild hepatic impairment based on National Cancer institute (NCI) classification (total bilirubin ≤Upper Limit of normal (ULN) and Aspartate Aminotransferase (AST) >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the pharmacokinetics (PK) of palbociclib.

Renal Impairment
A pharmacokinetic trial was conducted in subjects with varying degrees of renal function who were administered a single 125 mg dose of palbociclib. In this study, 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 ≥90mL/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 have not been studied in patients requiring hemodialysis.

Asian race
Data from a pharmacology study evaluating the effect of Japanese ethnicity on the PK of a single 125-mg oral palbociclib dose given to Japanese and non-Asian healthy volunteers indicate that palbociclib AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects when compared with non-Asian subjects. 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.

11 STORAGE, STABILITY AND DISPOSAL

Tablets: Store at 15˚C to 30˚C in the original blister pack to protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

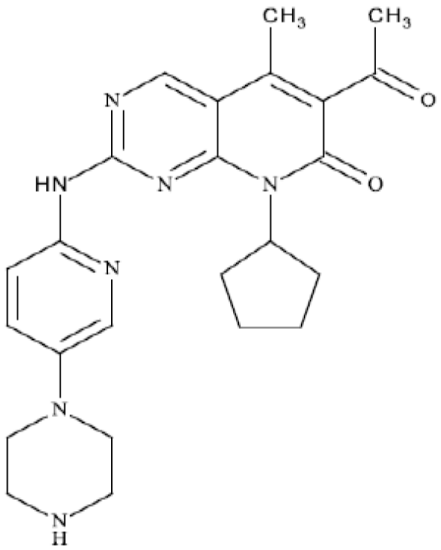
13 PHARMACEUTICAL INFORMATION

Drug Substance
Common name: Palbociclib

Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2- pyridinyl] amino]pyrido[2, 3-*d*]pyrimidin-7(8*H*)-one

Molecular formula and molecular mass: $C_{24}H_{29}N_7O_2$, 447.53 g/mol

Structural formula:



Physicochemical properties: Palbociclib is a yellow to orange powder with pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Palbociclib plus letrozole for the initial endocrine-based therapy of patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer

The efficacy of palbociclib in combination with letrozole was evaluated in an international, randomized, double-blind, parallel-group, multicenter Phase 3 study A5481008 (PALOMA-2) 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, defined as any lung, including pleura, and/or liver involvement versus non-visceral, namely sites different from lung, pleura, and liver), 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 (Schedule 3/1). Patients received study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Table 11. Summary of Demographic and Other Baseline Characteristics PALOMA-2 (Intent-to-Treat Population)

Characteristics	Palbociclib+Letrozole (N=444)	Placebo+Letrozole (N=222)
Age (years)		
Median (min-max)	62 (30-89)	61 (28-88)
<65, n (%)	263 (59.2)	141 (63.5)
≥65, n (%)	181 (40.8)	81 (36.5)
Race, n (%)		
White	344 (77.5)	172 (77.5)
Black	8 (1.8)	3 (1.4)
Asian	65 (14.6)	30 (13.5)
Other	27 (6.1)	17 (7.7)
ECOG performance status, n (%)		
0	257 (57.9)	102 (45.9)
1	178 (40.1)	117 (52.7)
2	9 (2.0)	2 (1.4)
Stage of disease at initial diagnosis		
Stage III	72 (16.2)	39 (17.6)

Characteristics	Palbociclib+Letrozole (N=444)	Placebo+Letrozole (N=222)
Stage IV	138 (31.1)	72 (32.4)
Disease-free interval, n (%)		
Newly metastatic disease	167 (37.6)	81 (36.5)
≤12months	99 (22.3)	48 (21.6)
>12 months	178 (40.1)	93 (41.9)
Disease site,[a] n (%)		
Visceral	214 (48.2)	110 (49.5)
Non visceral	230 (51.8)	112 (50.5)
Bone only	103 (23.2)	48 (21.6)
Prior systemic therapies, n (%)		
No	167 (37.6)	81 (36.5)
Yes	277 (62.4)	141 (63.5)
Number of regimens		
1	133 (30.0)	74 (33.3)
2	95 (21.4)	48 (21.6)
3	34 (7.7)	17 (7.7)
>3	15 (3.4)	2 (<1.0)
Previous chemotherapy regimen for primary diagnosis, n (%)		
No	231 (52.0)	113 (50.9)
Yes	213 (48.0)	109 (49.1)
Previous hormonal regimen for primary diagnosis, n (%)		
1	158 (35.6)	87 (39.2)
>1	91 (20.5)	39 (17.6)

ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; N=total number of patients in population; n=number of patients meeting prespecified criteria.
a. Based on randomization.

The primary efficacy objective of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Secondary endpoints included overall survival (OS) and objective response (OR). The final analysis, performed at a median follow-up time of 23.0 months in the palbociclib plus letrozole arm and 22.3 months in the placebo plus letrozole arm, indicated that patients treated with palbociclib plus letrozole had a statistically significant 42% reduction in the risk of progression compared to those treated with placebo plus letrozole. Data from an independent radiographic review was supportive of this treatment effect.

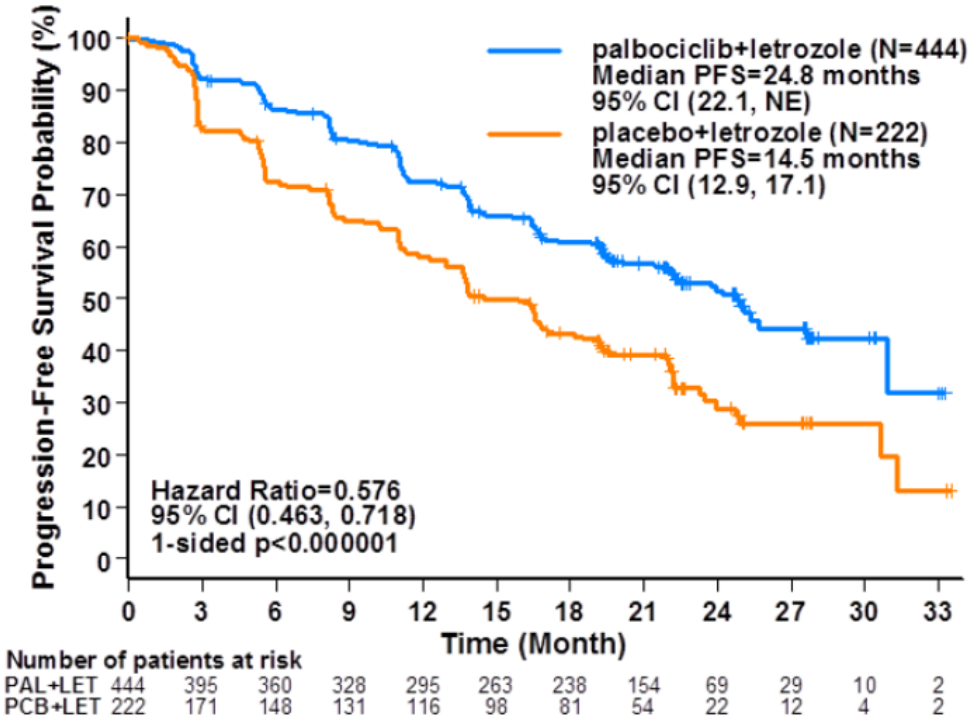
The results of the primary PFS analysis from PALOMA-2 are summarized in Table 12, and the Kaplan-Meier curve for PFS is shown in Figure 1.

Table 12. PALOMA-2 (Intent to treat population)-Progression-Free Survival Results

	Primary Analysis	
	Palbociclib plus Letrozole (N = 444)	**Placebo plus Letrozole (N = 222)**
Number of events (%)	194 (43.7)	137 (61.7)
Median PFS [months (95% CI)]	24.8 (22.1, NE)	14.5 (12.9, 17.1)
Hazard ratio [(95% CI) and p-value]	0.576 (0.463, 0.718), p<0.000001	

N=number of patients; CI=confidence interval; NE=not estimable; PFS=progression-free-survival.

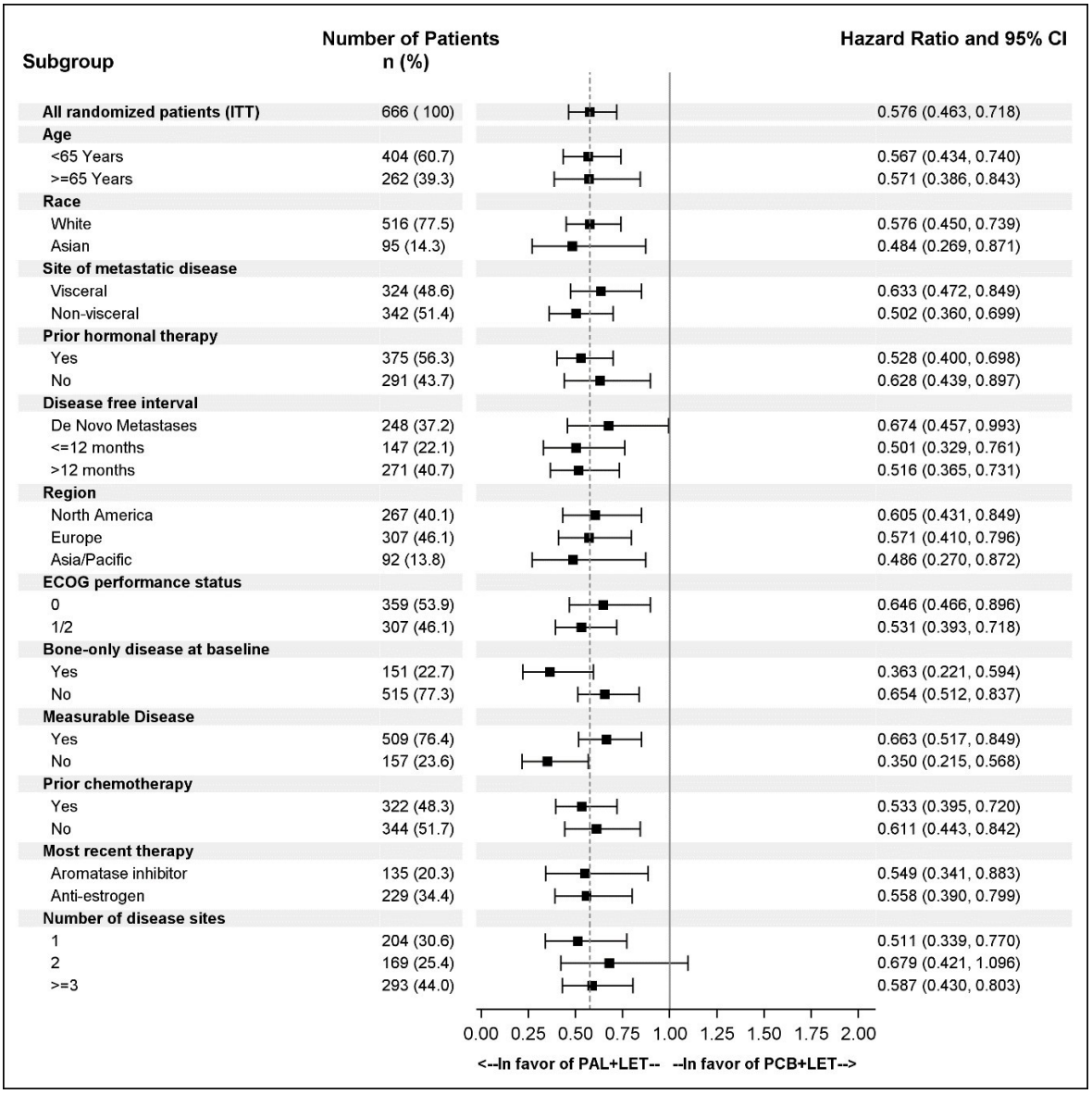
Figure 1. Kaplan-Meier Plot of Progression-Free Survival – PALOMA-2 (Investigator Assessment, Intent-to-Treat Population)



Abbreviations: CI=confidence interval; CSR=Clinical Study Report; LET =letrozole; N=number of patients; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression -free survival.

A series of prespecified subgroup PFS analyses was performed based on prognostic factors and baseline characteristics (see Figure 2). Consistent PFS results were observed across patient subgroups.

Figure 2. Forest Plot of Subgroup Analyses of Progression Free Survival – PALOMA-2 (Investigator Assessment, Intent-to-Treat Population)



Hazard ratio: Based on the Coxproportional hazards model, assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of palbociclib plus letrozole.
"Prior chemotherapy" and "Most recent therapy" were as (neo) adjuvant therapy.
"Most recent therapy" was as follows: Aromatase inhibitors=anastrozole, letrozole or exemestane, Anti-estrogens=tamoxifen, tamoxifen citrate, toremifene, toremifene citrate, or fulvestrant.
Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; LET=letrozole; ITT=intent - to-treat; n=number of patients in category; PAL=palbociclib; PCB=placebo.

Objective response rate in patients with measurable disease as assessed by the investigator was higher in the palbociclib plus letrozole arm compared to the placebo plus letrozole arm (60.7% versus 49.1%, Table 13). The overall survival (OS) data were not mature at the time of the final PFS analysis.

Table 13. Objective Response Rate–Confirmed Responses–PALOMA-2 (Investigator-Assessment–Intent-to-Treat Population)

	Palbociclib + Letrozole % (95% CI)	Placebo + Letrozole % (95% CI)
Patients with Measurable Disease	**N=338**	**N=171**
Objective Response Rate[b]		
Investigator-assessment[c]	60.7 (55.2, 65.9)	49.1 (41.4, 56.9)
Odds Ratio (95% Exact CI)	1.59 (1.08, 2.35)	
p-value[a]	0.0090	
Confirmed response	**n (%)**	**n (%)**
Complete response	9 (2.7)	4 (2.3)
Partial response	178 (52.7)	72 (42.1)
Stable/no response	116 (34.3)	59 (34.5)
Objective progression	25 (7.4)	28 (16.4)
Indeterminate	10 (3.0)	8 (4.7)

According to RECIST version 1.1.
Abbreviations: BICR=blinded independent central review; CI=confidence interval; CSR=Clinical Study Report; RECIST=Response Evaluation Criteria in Solid Tumors.
a: 1-sided p-value from exact test.
b: Objective response=complete response plus partial response.
c: 338 patients in the palbociclib plus letrozole arm and 171 patients in the placebo plus letrozole arm had measurable disease at baseline.

An updated analysis of the primary and secondary endpoints was performed after an additional 15 months of follow up (approx. 38 months in total). 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. The median PFS in the palbociclib plus letrozole arm was 27.6 (95% CI 22.4, 30.3) months vs 14.5 (95% CI 12.3, 17.1) months in the comparator arm with an HR of 0.563 (95% CI 0.461, 0.687, p<0.000001). At the time of this updated analysis, ORR for the ITT population with measurable disease was higher in the palbociclib plus letrozole arm (62.4%; 95% CI: 57.0, 67.6) compared with the placebo plus letrozole arm (49.7%; 95% CI: 42.0, 57.4).

After a median follow-up time of 90 months, the final OS analysis was performed based on 435 events (65.3% of randomized patients). Median OS in the palbociclib plus letrozole arm was 53.8 months compared to 49.8 months in the placebo plus letrozole arm (Hazard Ratio 0.921 [95% CI 0.755, 1.124], not statistically significant).

Palbociclib plus fulvestrant for the treatment of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed after prior endocrine therapy

The efficacy of palbociclib plus fulvestrant versus placebo plus fulvestrant was evaluated in an

international, randomized, double-blind, parallel-group, multicenter study (PALOMA-3) conducted in women with HR-positive/HER2-negative locally advanced or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy.

A total of 521 pre and 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. Fulvestrant 500 mg was administered to all patients as described in its Product Monograph. 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. Crossover between treatment arms was not allowed.

Baseline demographics and prognostic characteristics of the study population are shown in Table 12 below.

Table 14. Summary of Demographic and Other Baseline Characteristics PALOMA-3 (Intent-to- Treat Population)

Characteristics	**Palbociclib + Fulvestrant (N=347)**	**Placebo + Fulvestrant (N=174)**
Age (years)		
Median (min-max)	57 (30-88)	56 (29-80)
<65, n (%)	261 (75.2)	131 (75.3)
≥65, n (%)	86 (24.8)	43 (24.7)
Race, n (%)		
White	252 (72.6)	133 (76.4)
Black	12 (3.5)	8 (4.6)
Asian	74 (21.3)	31 (17.8)
Other	8 (2.3)	1 (0.6)
Unspecified	1 (0.3)	1 (0.6)
ECOG performance status, n (%)		
0	206 (59.4)	116 (66.7)
1	141 (40.6)	58 (33.3)
Documented sensitivity to prior hormonal therapy, [a] n (%)		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)

Characteristics	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
Visceral metastases,[a] n (%)		
Yes	206 (59.4)	105 (60.3)
No	141 (40.6)	69 (39.7)
Menopausal status[a,b] n (%)		
Pre-/peri-	72 (20.7)	36 (20.7)
Post-	275 (79.3)	138 (79.3)
Extent of Disease		
Locally advanced	69 (19.9)	47 (27.0)
Metastatic	86 (24.8)	36 (20.7)
Prior systemic therapies, n (%)		
No	0 (0)	0 (0)
Yes	347 (100)	174 (100)
Number of regimens		
1	71 (20.5)	39 (22.4)
2	106 (30.5)	56 (32.2)
3	98 (28.2)	35 (20.1)
>3	72 (20.7)	44 (25.3)
Prior lines of therapy in the metastatic setting:		
0	84 (24.2)	45 (25.9)
1	132 (38.0)	70 (40.2)
2	90 (25.9)	43 (24.7)
≥3	41 (11.8)	16 (9.2)
Previous chemotherapy regimen for primary diagnosis, n (%)		
No	95 (27.4)	37 (21.3)
Yes	252 (72.6)	137 (78.7)
Previous hormonal regimen for primary diagnosis, n (%)		
1	134 (38.6)	77 (44.3)
>1	213 (61.4)	97 (55.7)

ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; N=total number of patients in population; n=number of patients meeting prespecified criteria.

a. Based on randomization.

b. Postmenopausal status defined by at least 1 of the following criteria: 1) ≥60 years of age; 2) <60

Characteristics	Palbociclib + Fulvestrant (N=347)	Placebo + Fulvestrant (N=174)
years of age and cessation of regular menses for at least 12 consecutive months, with no alternative pathological or physiological cause, and serum estradiol and follicle stimulating hormone level within the laboratory's reference range for postmenopausal women; 3) documented bilateral oophorectomy; or 4) medically confirmed ovarian failure. Pre- or perimenopausal status defined as not meeting the criteria for being postmenopausal.		

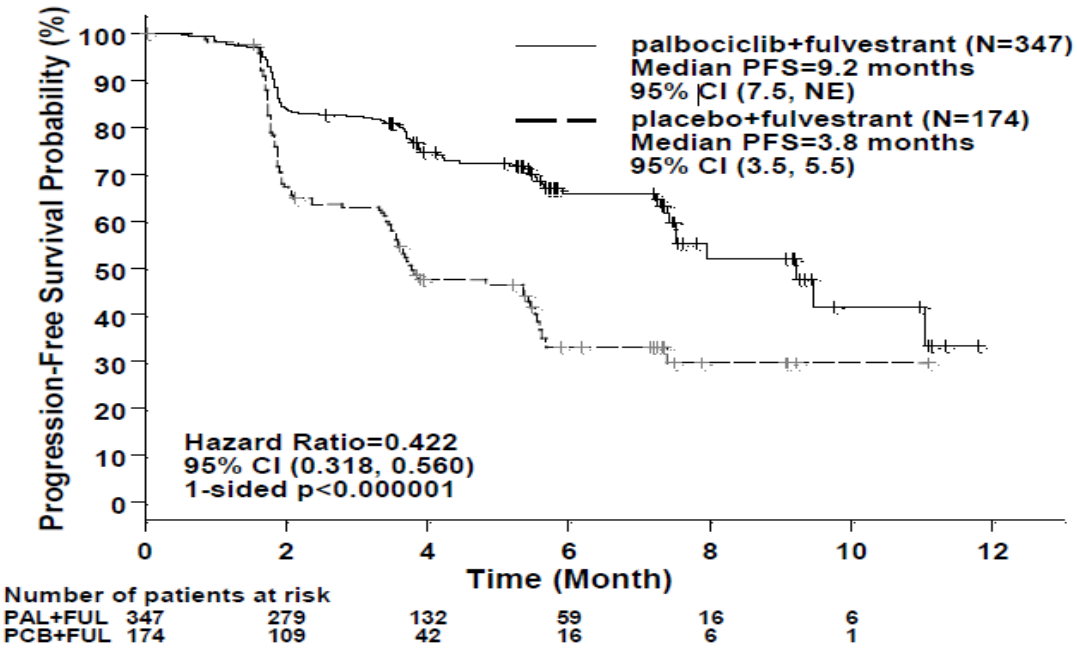
The primary endpoint of the study was investigator-assessed PFS, defined as the interval from randomization to the earlier of the first documentation of progressive disease or death from any cause, evaluated according to RECIST 1.1. Secondary endpoints included OS and objective response (OR). The primary analysis, performed at a median follow-up of 5.6 months, indicated that patients treated with palbociclib plus fulvestrant had a statistically significant 57% reduction in the risk of progression compared to those treated with placebo plus fulvestrant. Efficacy results for PALOMA-3 are shown below in Table 15, and the Kaplan-Meier curve for PFS is shown in Figure 4.

Table 15– Primary Efficacy Results–PALOMA-3 (Investigator Assessment, Intent-to-Treat Population)

	Palbociclib plus Fulvestrant (N=347)	Placebo plus Fulvestrant (N=174)
Progression-Free Survival		
Number of PFS Events (%)	102 (29.4%)	93 (53.4%)
Median PFS [months] (95% CI) at Interim Analysis	9.2 (7.5, NE)	3.8 (3.5, 5.5)
Hazard ratio (95% CI) and p- value	0.422 (0.318, 0.560), p<0.000001	

N=number of patients; CI=confidence interval; NE=not estimable; PFS = Progression-Free Survival;

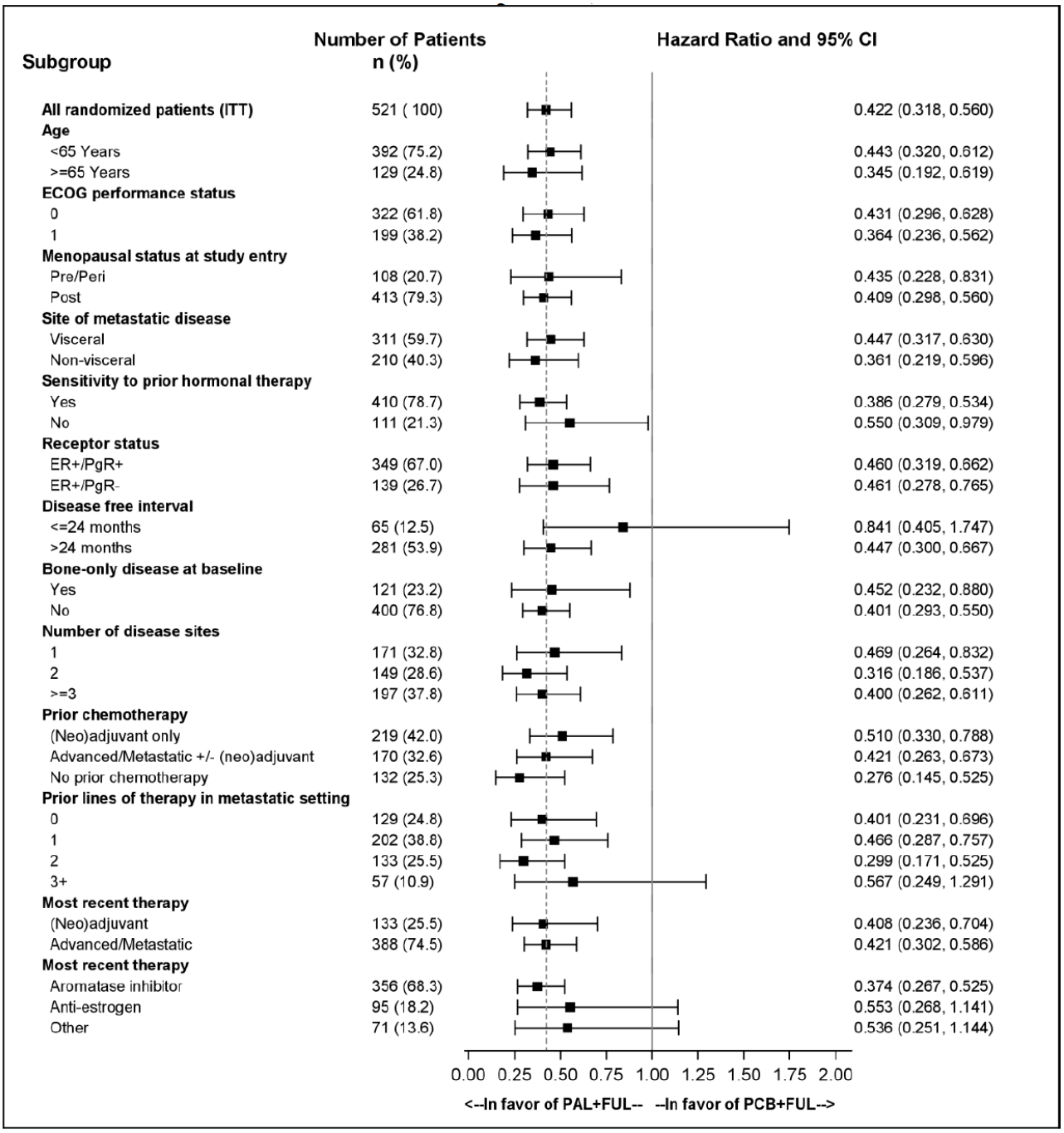
Figure 4. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3



Abbreviations: CI: confidence interval, FUL: fulvestrant, N: number of patients, PAL: palbociclib, PCB: placebo, PFS: progression-free survival, NE: not estimable

Consistent PFS results were observed across patient subgroups (see Figure 5).

Figure 5 Forest Plot of Subgroup Analyses of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population)–PALOMA-3



Abbreviations: CI: confidence interval, CRF: case report form, ECOG: Eastern Cooperative Oncology Group, ER+: estrogen receptor positive, ITT: intent-to-treat, FUL: fulvestrant, n: number of patients, PAL: palbociclib, PCB: placebo, PgR+/-: progesterone receptor positive/negative. Note: The HR (95% CI) provided for all randomized patients (ITT) is based on the stratified analysis

An updated PFS analysis, performed at median duration of follow-up of 15.8 months for patients treated with palbociclib plus fulvestrant, and 15.3 months for patients treated with

placebo plus fulvestrant, was consistent with the primary analysis results, and indicated a 50% reduction in the risk of progression in favor of palbociclib plus fulvestrant treatment over placebo plus fulvestrant (HR=0.497, 95% CI: 0.398, 0.620), with a median PFS of 11.2 months (95% CI: 9.5, 12.9) compared to 4.6 months (95% CI: 3.5, 5.6), respectively. At the time of this updated analysis, ORR for the ITT population with measurable disease was higher in the palbociclib plus fulvestrant arm (27.3%; 95% CI: 22.1, 33.1) compared with the placebo plus fulvestrant arm (10.9%; 95% CI: 6.2, 17.3).

At the time of final analysis of PFS, overall survival (OS) data were not mature. No survival benefit has been demonstrated.

The OS data were not mature at the time of the final PFS analysis (11% of patients had died). After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (59.5% of randomized patients). Median OS in the palbociclib plus fulvestrant arm was 34.9 months compared to 28 months in the placebo plus fulvestrant arm [Hazard Ratio 0.814 (95% CI 0.644, 1.029), not statistically significant].

14.2 Comparative Bioavailability Studies

A randomized, two treatment, two period, two way cross-over, single oral dose (1 x 125 mg) comparative bioavailability study of PrTARO-PALBOCICLIB tablets and PrIbrance® tablets was conducted in healthy, adult, subjects under fasting conditions. Data from the 31 subjects included in the statistical analysis are summarized below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Palbociclib (1 x 125 mg) Geometric Mean[5] Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means[5]**	**90% Confidence Interval**
AUC_T (ng•h/mL)	2052.66 2076.05 (22.41)	2067.70 2124.52 (23.79)	99.3	95.7 - 103.1
$AUC_{0\text{-}72h}$ (ng•h/mL)	1837.74 1880.86 (21.19)	1881.28 1927.55 (22.29)	97.7	93.4 - 102.2
AUC_I (ng•h/mL)	2087.80 2144.64 (23.15)	2130.12 2191.96 (24.68)	98.0	93.8 - 102.4
C_{max} (ng/mL)	71.46 71.86 (24.39)	69.71 71.75 (23.30)	102.5	96.9 - 108.5
T_{max}[3] (h)	6.00 (3.00 - 10.00)	6.50 (3.00 - 10.00)		

Palbociclib (1 x 125 mg) Geometric Mean[5] Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means[5]**	**90% Confidence Interval**
$T_{½}$[4] (h)	24.28 (13.27)	23.48 (13.95)		

[1] Taro-Palbociclib (palbociclib) tablets, 125 mg (Taro Pharmaceuticals Inc.)
[2] [Pr]Ibrance® (palbociclib) tablets, 125 mg (Pfizer Canada ULC)
[3] Expressed as median (range)
[4] Expressed as the arithmetic mean (CV%)
[5] Least square mean

A randomized, two treatment, two period, two way cross-over, single oral dose (1 x 125 mg) comparative bioavailability study of [Pr]Taro-Palbociclib tablets and Ibrance tablets was conducted with pre-treatment of Sandoz Rabeprazole [Rabeprazole Sodium Enteric-Coated Tablets 40 mg (20 mg x 2)] of Sandoz Canada Inc. in healthy, adult, subjects under fasting conditions. Data from the 54 subjects included in the statistical analysis are summarized below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Palbociclib (1 x 125 mg) Geometric Mean[5] Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means[5]**	**90% Confidence Interval**
AUC_T (ng•h/mL)	1862.65 1940.40 (27.46)	2203.85 2243.78 (18.84)	84.5	81.0 – 88.2
$AUC_{0\text{-}72h}$ (ng•h/mL)	1666.13 1737.32 (27.76)	1973.22 2008.78 (18.78)	84.4	80.9 - 88.8
AUC_I (ng•h/mL)	1937.24 2017.03 (27.27)	2289.60 2330.53(18.70)	84.6	81.1 - 88.2
C_{max} (ng/mL)	55.40 58.95 (33.33)	66.53 68.17 (22.21)	83.3	78.4 - 88.5
T_{max}[3] (h)	7.50 (3.00 - 11.00)	7.50 (2.00 - 11.00)		
$T_{½}$[4] (h)	25.19 (12.42)	24.98 (13.11)		

[1] Taro-Palbociclib tablets, 125 mg (Taro Pharmaceuticals Inc.)
[2] [Pr]Ibrance® (palbociclib) tablets, 125 mg (Pfizer Canada ULC)

[3] Expressed as median (range)
[4] Expressed as the arithmetic mean (CV%)
[5] Least square mean

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The primary target organ findings of potential relevance to humans included haematolymphopoietic and male reproductive organ effects in rats and dogs in studies up to 39 weeks duration. Effects on glucose metabolism were associated with findings in the pancreas and secondary effects on eye, kidney, and adipose tissue in studies ≥15 weeks duration in rats only and bone and teeth changes were observed in rats only following 27 weeks of dosing. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. The reversibility of the effects on glucose homeostasis, pancreas, eye, kidney, and bone was not established following a 12-week nondosing period, whereas partial to full reversal of effects on the haematolymphopoietic and male reproductive systems, teeth, and adipose tissue was observed.

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 60mg/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.

Reproductive and Developmental Toxicology: In a fertility study in female rats, palbociclib did not affect mating or fertility 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 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 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, respectively. Partial reversibility of male reproductive organ effects was observed in the rat and dog following a 4- and 12-week nondosing 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 the human clinical exposure based on AUC; however, the females that mated with males in this group had lower pregnancy rates (88.9%) compared to the females that successfully mated with males from the lower dose and control groups (100%).

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Ibrance® (palbociclib tablets, 75 mg, 100 mg and 125 mg), submission control 287136, Product Monograph, Pfizer Canada ULC. (SEP 04, 2024)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTARO-PALBOCICLIB

Palbociclib Tablets

Read this carefully before you start taking **TARO-PALBOCICLIB** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TARO-PALBOCICLIB**.

Your breast cancer will be treated with **TARO-PALBOCICLIB** in combination with another family of medications, called aromatase inhibitors or with fulvestrant. Read the Patient Medication Information leaflet for the other medication carefully as well as this one.

Serious Warnings and Precautions

Take TARO-PALBOCICLIB under the care of a healthcare professional who knows how to use anti-cancer drugs.

TARO-PALBOCICLIB can cause the following serious side effect:

- **Neutropenia:** abnormally low number of white blood cells in your blood.

What is TARO-PALBOCICLIB used for?

TARO-PALBOCICLIB is a prescription medicine. It is used in pre/peri-menopausal or post-menopausal women, or men, to treat hormone receptor positive breast cancer that has spread to other parts of the body. It is used with:

- aromatase inhibitors
- fulvestrant: to treat patients whose breast cancer has failed other hormone treatments.

Pre or peri-menopausal women (women who have not gone through menopause) and men treated with a combination of TARO-PALBOCICLIB and aromatase inhibitors and pre/perimenopausal women treated with a combination of TARO-PALBOCICLIB and fulvestrant should also be treated with a medicine that lowers the amount of sex hormones made by the body luteinizing hormone releasing hormone (LHRH) agonist).

How does TARO-PALBOCICLIB work?

Palbociclib belongs to a family of medications called kinase inhibitors. These medications work by stopping cancer cells from dividing and growing. When given together with an aromatase inhibitor or fulvestrant, TARO-PALBOCICLIB may slow down the growth and spread of breast cancer cells.

What are the ingredients in TARO-PALBOCICLIB Tablets?

Medicinal ingredients: Palbociclib

Non-medicinal ingredients: Anhydrous citric acid, colloidal silicon dioxide, crospovidone,

magnesium stearate, microcrystalline cellulose, sodium stearyl fumarate, succinic acid.

Film coating material:
75 mg and 125 mg tablets: FD&C blue #2, hypromellose, iron oxide red, titanium dioxide, and triacetin.
100 mg tablets: FD&C blue #2, hypromellose, iron oxide yellow, titanium dioxide, and triacetin.

TARO-PALBOCICLIB comes in the following dosage forms:
Tablets: 75 mg, 100 mg, 125 mg

Risk of medication error: Be sure to follow the directions on how to take TARO-PALBOCICLIB tablets. These can be taken with or without food.

Do not use TARO-PALBOCICLIB if:

- you are allergic to palbociclib or any of the other ingredients of TARO-PALBOCICLIB.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO-PALBOCICLIB. Talk about any health conditions or problems you may have, including if you:

- have fever, chills, or any other signs or symptoms of infection
- have heart problems, including a condition called long QT syndrome
- have liver or kidney problems
- have any other medical conditions

Other warnings you should know about:

TARO-PALBOCICLIB may cause:

- **Serious or life-threatening infections**. Your healthcare professional will decide when to perform blood tests and will interpret the results.
- **Neutropenia and Leukopenia (low white blood cells).**
- **Anemia (low red blood cells)**
- **Lung problems (pneumonitis):** severe or life-threatening inflammation of the lungs during treatment that can lead to death.
- **Blood clots (venous thromboembolism)**: in the lungs, arms or legs.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy, Breastfeeding and Fertility:

Women:

- TARO-PALBOCICLIB should only be used in women who are postmenopausal or women who have not gone through menopause when used with a medicine to stop their ovaries from making estrogen.
- TARO-PALBOCICLIB should not be taken during pregnancy. Talk to your healthcare professional if you are pregnant, think you might be pregnant or plan to become pregnant. TARO-PALBOCICLIB may harm your unborn baby.

- If you are able to become pregnant and are taking TARO-PALBOCICLIB, you should use effective birth control during treatment and for at least 21 days after the final dose. Talk to your healthcare professional about the birth control options that may be right for you.
- Talk to your healthcare professional if you are breastfeeding or planning to breastfeed. It is not known if TARO-PALBOCICLIB passes into breast milk. You and your healthcare professional should decide if you will take TARO-PALBOCICLIB or breastfeed. You should not do both.

Men:

- If you are a male patient with a female partner who is able to become pregnant, you should use effective birth control during treatment with TARO-PALBOCICLIB and for at least 97 days after the final dose.
- TARO-PALBOCICLIB may affect fertility in men. Male patients should talk to their healthcare professional about sperm preservation before they start therapy with TARO-PALBOCICLIB.

TARO-PALBOCICLIB should not be used in children and adolescents under 18 years of age.

Driving and using machines: Fatigue and dizziness can occur with TARO-PALBOCICLIB. Give yourself time after taking TARO-PALBOCICLIB to see how you feel before driving or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TARO-PALBOCICLIB:

- medicines for bacterial infections (antibiotics), such as clarithromycin, nafcillin, rifampin and telithromycin
- medicines for fungal infections, such as ketoconazole, itraconazole, posaconazole and voriconazole
- some medicines for high blood pressure, such as bosentan
- HIV medicines, such as saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, efavirenz and etravirine
- antiviral medicines, such as telaprevir
- antidepressant medicines, such as nefazodone
- medicines to treat epilepsy, such as carbamazepine and phenytoin
- medicines to treat certain types of sleep disorders, such as modafinil
- St. John's wort, an herbal medicine used to treat depression
- grapefruit. Do not drink grapefruit juice or eat grapefruit, or products containing grapefruit extracts, star fruit, pomegranate, Seville oranges or other similar fruits. They may change the amount of TARO-PALBOCICLIB in your body.

Other drugs not listed here may also interact with TARO-PALBOCICLIB

How to take TARO-PALBOCICLIB Tablets

Always take TARO-PALBOCICLIB tablets exactly as your healthcare professional tells you. Your

healthcare professional might adjust your dose if you have certain side effects. Do not change your dose or stop TARO-PALBOCICLIB unless told to do so by your healthcare professional. Check with your healthcare professional if you are not sure.

Be sure the pharmacist has provided **tablets** for you.

- **Take with or without food** once a day for 21 days. This is followed by 7 days off (3 weeks on, 1 week off) for a 28 day cycle.
- Swallow whole. Do NOT chew, crush or split the tablets. Do NOT take tablets if they are broken, cracked or look damaged.
- Take your dose of TARO-PALBOCICLIB at approximately the same time each day.
- If you vomit after taking a dose of TARO-PALBOCICLIB, do not take an extra dose. Take your next dose at your regular time.

Recommended starting dose: 125 mg

Usual Adult dose:

Tablet: 1 tablet once a day with or without food for 21 days followed by 7 days with no TARO-PALBOCICLIB treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much TARO-PALBOCICLIB contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a day's dose, do not take an extra dose the next day. Take your next dose at your regular time.

What are possible side effects from using TARO-PALBOCICLIB?

These are not all the possible side effects you may have when taking TARO-PALBOCICLIB. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- shortness of breath
- tiredness or weakness
- cough
- mouth sores
- unusual hair thinning or loss
- nausea, vomiting
- bruising
- loss of appetite
- tingling or abnormal feeling (especially in arms and legs)
- nose bleed
- headache
- constipation

- rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (low level of red blood cells)**:** fatigue, loss of energy, weakness, shortness of breath		√	
Infections: fever, chills, dizziness, weakness, shortness of breath		√	
Neutropenia and Leukopenia (low level of white blood cells)**:** infection, fever		√	
COMMON			
Diarrhea	√		
Fever		√	
Palmar-plantar erythrodysaesthesia syndrome (also called Hand-Foot syndrome): red or swollen palms, thick calluses and blisters of the hands and soles of the feet, tingling or burning, tightness of the skin		√	
Thrombocytopenia (low level of blood platelets)**:** increased tendency to bruise or bleed		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Venous thromboembolism (blood clots): • **Pulmonary embolism** (lung): chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath • **Deep vein thrombosis** (arm or leg): swelling, pain, arm or leg may be warm to the touch and may appear red			√
RARE			
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning skin, fever		√	
UKNOWN			
Lung problems (pneumonitis): trouble breathing or shortness of breath, cough with or without mucus, chest pain.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Tablets: Store at 15°C to 30°C in the original blister pack to protect from moisture.

Keep out of reach and sight of children.

If you want more information about TARO-PALBOCICLIB:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.taro.ca, or by contacting the sponsor, Taro Pharmaceuticals Inc. at 1-800-268-1975.

This leaflet was prepared by

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