Palbrance®

Palbociclib

FORMS AND PRESENTATION

Palbrance® 75: Capsules. Box of 21.
Palbrance® 100: Capsules. Box of 21.
Palbrance® 125: Capsules. Box of 21.

COMPOSITION

Palbrance® 75: Each capsule contains Palbociclib 75mg.
Palbrance® 100: Each capsule contains Palbociclib 100mg.
Palbrance® 125: Each capsule contains Palbociclib 125mg.
Excipients: microcrystalline cellulose, dibasic calcium phosphate dihydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, iron oxide red, iron oxide yellow, titanium dioxide, gelatin, sodium lauryl sulfate, shellac, black iron oxide, potassium hydroxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking the progression of the cell from G1 into the S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly ER-positive breast cancers.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time-matched electrocardiogram (ECG) evaluating the change from baseline and corresponding pharmacokinetic data in patients with advanced breast cancer. Palbociclib did not prolong the QTc to any clinically relevant extent at the recommended dose of 125 mg daily.

Pharmacokinetic properties

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

Absorption

The C_{max} of palbociclib is generally observed between 4 to 12 hours (time to reach maximum concentration [T_{max}]) following oral administration. The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the area under the curve (AUC) and C_{max} increase proportionally with the 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).

Distribution

The binding of palbociclib to human plasma proteins *in vitro* was ~85%, with no concentration dependence. The mean fraction unbound (f_u) of palbociclib in human plasma in vivo increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib f_u in human plasma in vivo with worsening renal function. *In vitro*, the uptake of palbociclib into human hepatocytes occurred mainly via passive diffusion. Palbociclib is not a substrate of OATP1B1 or OATP1B3.

Biotransformation

Palbociclib undergoes extensive hepatic metabolism in humans. Following oral administration, the major primary metabolic pathways for palbociclib involved oxidation and sulphonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma. The majority of the material was excreted as metabolites. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulphotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63 L/h, and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{14}C]palbociclib, a median of 92% of the total administered radioactive dose was recovered in 15 days; feces (74% of dose) was the major route of excretion, with 17% of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2% and 7% of the administered dose, respectively.

Special Populations

Pediatric population

The pharmacokinetics of palbociclib has not been evaluated in patients < 18 years of age.

Hepatic impairment

A pharmacokinetic study in subjects with varying degrees of hepatic function indicates that palbociclib unbound exposure (unbound AUC_{inf}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) was increased by 7%, 38%, and 72% for mild, moderate, and severe hepatic impairment, respectively, relative to subjects with normal hepatic function.

Renal impairment

Data from a pharmacokinetic study in subjects with varying degrees of renal function indicate that total palbociclib exposure (AUC_{inf}) increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl < 90 mL/min), moderate (30 mL/min ≤ CrCl < 60 mL/min), and severe (CrCl < 30 mL/min) renal impairment, respectively, relative to subjects with normal (CrCl ≥ 90 mL/min) renal function. Peak palbociclib exposure (C_{max}) was increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

INDICATIONS

Palbrance® is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

CONTRAINDICATIONS

Palbociclib is contraindicated in case of:

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

PRECAUTIONS

Pre/perimenopausal women

Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered palbociclib in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

Critical visceral disease

The efficacy and safety of palbociclib have not been studied in patients with critical visceral disease.

Hematological disorders

Dose 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.

Interstitial lung disease (ILD)/pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with palbociclib when taken in combination with endocrine therapy. 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, palbociclib should be immediately interrupted and the patient should be evaluated. Palbociclib should be permanently discontinued in patients with severe ILD or pneumonitis.

Infections

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

Patients should be monitored for signs and symptoms of infection and treated as medically appropriate. Physicians should inform patients to promptly report any episodes of fever.

Hepatic impairment

Palbociclib should be administered with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity.

Renal impairment

Palbociclib should be administered with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity.

Concomitant treatment with inhibitors or inducers of CYP3A4

Strong inhibitors of CYP3A4 may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Coadministration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the palbociclib dose to 75 mg once daily. When the strong inhibitor is discontinued, the dose of palbociclib should be increased (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for the coadministration of palbociclib with moderate CYP3A inducers.

Effects on ability to drive and use machines

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

PREGNANCY AND LACTATION

Women of childbearing potential/Contraception in males and females

Females of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods (e.g., double-barrier contraception) during therapy and for at least 3 weeks or 14 weeks after completing therapy for females and males, respectively.

Pregnancy

There is no or limited amount of data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity. Palbociclib is not recommended during pregnancy.

Breast-feeding

It is unknown whether palbociclib is excreted in human milk. Patients receiving palbociclib should not breastfeed.

DRUG INTERACTIONS

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

Effects of other medicinal products on the pharmacokinetics of palbociclib

Effect of CYP3A inhibitors

The concomitant use of strong CYP3A inhibitors including, but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, increased palbociclib total exposure (AUC_{inf}) and the peak concentration (C_{max}), hence it should be avoided. No dose adjustments are needed for mild and moderate CYP3A inhibitors.

Effect of CYP3A inducers

The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort decreased palbociclib AUC_{inf} and C_{max}, hence it should be avoided.

No dose adjustments are required for moderate CYP3A inducers such as modafinil.

Effect of acid-reducing agents

Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg palbociclib tablet 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.

Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, no clinically relevant effect of H2-receptor antagonists or local antacids on palbociclib exposure is expected.

Effects of palbociclib on the pharmacokinetics of other medicinal products

Palbociclib is a weak, time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state. Coadministration of multiple doses of palbociclib with midazolam increased the midazolam AUC_{inf} and C_{max} values.

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The dose of sensitive CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced when coadministered with palbociclib as palbociclib may increase their exposure.

Drug-drug interaction between palbociclib and letrozole

There is no drug interaction between palbociclib and letrozole when the 2 medicinal products were coadministered.

Effect of tamoxifen on palbociclib exposure

Palbociclib exposures were comparable when a single dose of palbociclib was coadministered with multiple doses of tamoxifen and when palbociclib was given alone.

Drug-drug interaction between palbociclib and fulvestrant

There is no clinically relevant drug interaction between palbociclib and fulvestrant when the two medicinal products were coadministered.

In vitro studies with transporters

Based on *in vitro* data, palbociclib is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of palbociclib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g., pravastatin, rosuvastatin, sulfasalazine) may increase their therapeutic effect and adverse reactions.

Palbociclib may inhibit the uptake transporter organic cationic transporter OCT1 and then may increase the exposure of medical product substrates of this transporter (e.g., metformin).

ADVERSE EFFECTS

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

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.

Infections and infestations: infections (very common).

Blood and lymphatic system disorders: neutropenia, leukopenia, anemia, thrombocytopenia (very common); febrile neutropenia (common).

Metabolism and nutrition disorders: decreased appetite (very common).

Nervous system disorders: dysgeusia (common).

Eye disorders: blurred vision, increased lacrimation, dry eye (common).

Respiratory, thoracic, and mediastinal disorders: epistaxis, ILD/pneumonitis (common).

Gastrointestinal disorders: stomatitis, nausea, diarrhea, vomiting (very common).

Skin and subcutaneous tissue disorders: rash, alopecia, dry skin (very common); cutaneous lupus erythematosus (uncommon).

General disorders and administration site conditions: fatigue, asthenia, pyrexia (very common).

Investigations: ALT increased, AST increased (very common).

Laboratory abnormalities observed in a pooled dataset from 3 randomized studies:

white blood cells decreased, neutrophils decreased, anemia, platelets decreased, AST increased, ALT increased.

DOSAGE AND ADMINISTRATION

Treatment with Palbrance® should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

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

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

When coadministered with Palbrance®, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter. Please refer to the Summary of Product Characteristics of fulvestrant.

Prior to the start of treatment with the combination of Palbrance® plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

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

Dose adjustments

Dose modification of Palbrance® is recommended based on individual safety and tolerability.

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

Table 1. Palbrance® recommended dose modifications for adverse reactions

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

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

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

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

Table 2. Palbrance® dose modification and management – Hematological toxicities

CTCAE grade	Dose modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3 Applies to all hematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections)	Day 1 of cycle: Withhold Palbrance®, until recovery to Grade ≤ 2, and repeat complete blood count monitoring within 1 week. When recovered to Grade ≤ 2, start the next cycle at the *same dose*. Day 15 of first 2 cycles: If Grade 3 on Day 15, continue Palbrance® at the *current* dose to complete the cycle and repeat the complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (> 1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 ANC (< 1,000 to 500/mm^3) + Fever ≥ 38.5 °C and/or infection	At any time: Withhold Palbrance® until recovery to Grade ≤ 2 Resume at the next lower dose.
Grade 4	At any time: Withhold Palbrance® until recovery to Grade ≤ 2 Resume at the next lower dose.
Grading according to CTCAE 4.0. ANC=absolute neutrophil counts; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.	
ANC: Grade 1: ANC < LLN – 1,500/mm^3; Grade 2: ANC 1,000 - < 1,500/mm^3; Grade 3: ANC 500 - < 1,000/mm^3; Grade 4: ANC < 500/mm^3.	

Table 3. Palbrance® dose modification and management – Non-haematological toxicities

CTCAE grade	Dose modifications
Grade 1 or 2	No dose adjustment is required
Grade ≥ 3 non-haematological toxicity (if p ersisting despite medical treatment)	Withhold until symptoms resolve to: • Grade ≤ 1 • Grade ≤ 2 (if not considered a safety risk for the patient) Resume at the next lower dose.
Grading according to CTCAE 4.0. CTCAE=Common Terminology Criteria for Adverse Events.	

Palbrance® should be permanently discontinued in patients with severe interstitial lung disease (ILD)/pneumonitis.

Special populations

Elderly

No dose adjustment of Palbrance® is necessary for patients ≥ 65 years of age.

Hepatic impairment

No dose adjustment of Palbrance® 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 Palbrance® is 75 mg once daily on Schedule 3/1.

Renal impairment

No dose adjustment of Palbrance® 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 dose adjustment recommendation in this patient population.

Pediatric population

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

Method of administration

Palbrance® is for oral use. Palbrance® must be taken with food. Palbociclib should not be taken with grapefruit or grapefruit juice.

Palbrance® capsules should be swallowed whole (should not be chewed, crushed, or split prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

OVERDOSAGE

In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and hematological (e.g., neutropenia) toxicity may occur and general supportive care should be provided.

STORAGE CONDITIONS

Store below 30°C

Keep in original pack in intact conditions.

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Marketing Authorization Holder
Benta S.A.L - Lebanon
Manufacturer
Manufactured by Alembic Pharmaceuticals Limited, India
For **Benta S.A.L. - Lebanon**