

DRUG NAME: Palbociclib**SYNONYM(S):** PD 0332991; PD 991; PF 332991¹**COMMON TRADE NAME(S):** IBRANCE®**CLASSIFICATION:** molecular targeted therapy*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Palbociclib is an orally administered, selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. CDK 4/6 form complexes with cyclin D to promote phosphorylation of retinoblastoma (Rb) protein, which allows cell cycle progression. Palbociclib is cell cycle phase-specific, blocking transition from the G1 to the S phase by binding to CDK 4/6 to inhibit Rb protein phosphorylation. Palbociclib is an immunosuppressive agent.^{1,2}

PHARMACOKINETICS:

Oral Absorption	C _{max} 4-8 hours; 46% mean absolute bioavailability; food intake reduces variability of exposure	
Distribution	penetrates extensively into peripheral tissues ^{1,2}	
	cross blood brain barrier?	yes; low penetration due to efflux pump activity ³
	volume of distribution	2583 L
	plasma protein binding	85%
Metabolism	extensive hepatic metabolism; mainly via CYP3A and sulfotransferase (SULT) 2A1 enzymes ^{1,4}	
	active metabolite(s)	no information found
	inactive metabolite(s)	glucuronide and sulfamic acid conjugates
Excretion	primarily as metabolites in feces ¹	
	urine	17.5% (6.9% as unchanged drug)
	feces	74.1% (2.3% as unchanged drug)
	terminal half life	29 hours
	clearance	63.1 L/h
Ethnicity	AUC and C _{max} are reported to be 30% and 35% higher for Japanese patients compared to non-Japanese patients	

Adapted from standard reference⁵ unless specified otherwise.**USES:****Primary uses:**

*Breast cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:**Special populations:**

- patients 65 years or older may be more likely than younger patients to experience neutropenia and leukopenia⁶

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Palbociclib is aneugenic in mammalian *in vitro* and *in vivo* chromosome tests, but not clastogenic in human lymphocytes *in vitro*.⁵

Fertility: In animal studies, testicular degeneration and secondary effects on the epididymis (hypospermia), prostate (atrophy), and seminal vesicles (decreased secretion) were observed in males. Reproductive organ effects were partially reversible after discontinuing palbociclib. There were no reported adverse effects on the estrous cycle or mating and fertility in females.^{4,5} Consider sperm preservation for male patients prior to beginning palbociclib.⁵

Pregnancy: In animal studies, palbociclib was fetotoxic at one to four times the expected human clinical exposure. Reduced fetal body weights and changes in skeletal ossification were observed.⁵ Females of childbearing potential should use effective contraception during treatment and for at least three weeks after completing therapy.⁵ Male patients should use effective contraception during treatment and for three months after completing therapy.⁷

Breastfeeding is not recommended during treatment and for three weeks after completing therapy due to the potential secretion into breast milk.⁷

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.^{8,9}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
blood and lymphatic system/ febrile neutropenia	<i>anemia</i> (30-78%, severe 3-6%) ^{5,10} ; may require treatment interruption/dose reduction
	febrile neutropenia (1%) ^{5,6,10}
	leukopenia (43-53%, severe 19-30%) ^{5,10} ; may require treatment interruption/dose reduction
	<i>neutropenia</i> (75-83%, severe 54-66%) ^{5,10} ; see paragraph following Side Effects table
	<i>thrombocytopenia</i> (17-23%, severe 2%) ^{5,10}
eye	blurred vision (6%) ¹⁰
	dry eye syndrome (4%) ¹⁰
	lacrimation increase (6%) ¹⁰
gastrointestinal	<i>emetogenic potential: rare</i> ^{8,11}
	diarrhea (21-24%, severe 4%) ^{5,10}
	nausea (25-34%, severe 2%) ^{5,10}
	stomatitis (25-28%) ^{5,10}
	vomiting (15-19%) ^{5,10}
general disorders and	asthenia (8-13%, severe 2%) ^{5,10}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
administration site conditions	fatigue (41%, severe 4%)
	pyrexia (8-13%) ^{5,10}
infections and infestations	infection (47-55%, severe 5%) ^{5,10}
	upper respiratory infection (31%, severe 1%)
metabolism and nutrition	appetite decrease (16%, severe 1%)
nervous system	dysgeusia (7%)
	headache (26%) ¹⁰
	peripheral neuropathy (13%)
respiratory, thoracic and mediastinal	epistaxis (7-11%) ^{5,10}
skin and subcutaneous tissue	alopecia (18-22%) ^{5,10}
	dry skin (6%) ¹⁰
	rash (17%) ¹⁰
vascular	pulmonary embolism (1-5%) ^{5,10}

Adapted from standard reference⁵ unless specified otherwise.

Neutropenia is commonly reported and can occur from cycle 1 onward. The median time to first neutropenic episode is 15 days, with a median duration of seven days for grade 3 or greater neutropenia. Unlike neutropenia associated with traditional chemotherapy, neutropenia induced by palbociclib is reversible, noncumulative, and is not commonly associated with fever. Studies show a reversible dormancy in healthy bone marrow progenitor cells with no decrease in total marrow cellularity or viability, meaning the cells are functional even if their replication is suppressed.^{1,3} Palbociclib treatment may need to be interrupted, delayed, and/or dose reduced for grade 3 or 4 neutropenia and/or infection.^{5,6}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice ⁵	may increase plasma level of palbociclib	may inhibit CYP 3A4 metabolism of palbociclib in the intestinal wall	avoid grapefruit juice for 48 hours before and during palbociclib therapy
itraconazole ^{5,7}	palbociclib AUC increased by 87% and C _{max} by 34%	strong inhibition of CYP3A by itraconazole	avoid concurrent use ⁵ ; if co-administration cannot be avoided, consider palbociclib dose reduction to 75 mg once daily ⁷
rifampin ⁵	palbociclib AUC decreased by 85% and C _{max} by 70%	strong induction of CYP3A by rifampin	avoid concurrent use
modafinil ^{5,7}	palbociclib AUC decreased by 32% and C _{max} by 11%	moderate induction of CYP3A by modafinil	no dose adjustment required for palbociclib ⁶

Children: safety and effectiveness not established in children

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