Palbociclib

Ibrance®

Mechanism of Action

According to the FDA NDA 207103, palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Treatment of breast cancer cell lines with the combination of palbociclib and antiestrogens leads to decreased retinoblastoma (Rb) protein phosphorylation resulting in reduced E2F expression and signaling, and increased growth arrest compared to treatment with each drug alone. In vitro treatment of ER-positive breast cancer cell lines with the combination of palbociclib and antiestrogens led to increased cell senescence compared to each drug alone, which was sustained for up to 6 days following palbociclib removal and was greater if antiestrogen treatment was continued. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling, and tumor growth compared to each drug alone.

Human bone marrow mononuclear cells treated with palbociclib in the presence or absence of an anti-estrogen in vitro did not become senescent and resumed proliferation following palbociclib withdrawal.

Toxicology

According to the FDA NDA 207103:

MULTIPLE doses: In beagles given a **15-week** study of orally administered daily palbociclib (via gavage) at either **0.2, 0.6, or 2 mg/kg/day (dosing schedule of once daily for 3 weeks, followed by a 1-week off dose period**, repeated up to 4 times, followed by a 4-week recovery period), severe toxicity was not observed. Target organ effects were observed in the thymus (grossly small, decreased cellularity), bone marrow (hypocellularity), gut-associated lymphoid tissue (decreased cellularity), testes (grossly small, degeneration of seminiferous tubules), and epididymides (grossly small, hypospermia). All effects observed on Day 106 (end of the treatment period) had partially or completely reversed by the end of the recovery period, with the exception of effects on the testes and epididymides.

- Clinical Signs: A slight dose-related increase in the incidence of soft stools and red/swollen pinna(e) was noted at 2 mg/kg/day compared to the controls.
- CBC: "Dose-related decreases in red blood cell parameters, decreases in leukocytes including neutrophil, lymphocyte, monocyte, and eosinophil counts, and decreases in platelets were observed at the end of each dosing period in both sexes. The magnitudes of decreases were similar on day 21, 46, and 106 (ends of dosing periods). The observed

changes recovered at least partially on Day 28, following a 1-week off dose period. After a 4-week recovery period, all findings had recovered in males and females."

- Chemistry: "unremarkable"
- Urinalysis: "unremarkable"

In a 39-week oral gavage study in Beagles at either 0.2, 0.6, or 3 mg/kg/day (dosing schedule of once daily for 3 weeks followed by 1 week off, repeated 10 times, followed by a 12-week recovery period), there were no new toxicities.

Significant respiratory effects were observed in dogs at 5 mg/kg, including apnea, transient increases in minute volume and respiratory rate, and decreases in compliance, peak expiratory flow, and tidal volume. The effect on respiratory function was observed at an unbound C_{max} ≥ 842 ng/mL (which is ~50 times the human clinical exposure at 125 mg QD based on mean unbound C_{max} 17 ng/mL). Treatment-related cardiovascular effects included increases in QT, QTc interval at ≥ 3 mg/kg with systemic exposure at ~4 times the human clinical exposure. Decreases in heart rate, increases in respiratory rate, and increases in systolic blood pressure were observed at 10 and 30 mg/kg between 4.5 and 20 hours post dose (with the systemic exposure >8 times human clinical exposure).

FDA Labeled Use

Ibrance® is not labeled for dogs; therefore use of this drug in the dog is off-label.

According to the FDA's Highlights of Prescribing Information (Reference ID 4514390):
Ibrance® is a kinase inhibitor indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

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

Selected Canine Publications

:: Preclinical

- Two cancer cell lines derived from canine oral squamous cell carcinoma (SCC1 and CoSCC) showed high sensitivity to palbociclib, which induced a significant increase in the number of cells both in early and/or late apoptosis along with a concomitant decrease in viable cells. This study identified CDK4/6 overexpression as a potential therapeutic vulnerability in canine oral squamous cell carcinoma, warranting further interrogation in the clinical setting (Guscetti et al.).

- Two canine mammary tumor (CMT) cell lines with endogenous CDK4/6 co-expression (P114 and CF41) treated with palbociclib resulted in a dose- and time-dependent loss of phosphorylated retinoblastoma protein (pRb). Moreover, treatment of CMT cells with palbociclib-induced cell cycle arrest affected cell viability, prevented colony formation, and impaired cell migration activity. Palbociclib also inhibited the growth of P114 and CF41 cell spheroids (Schoos et al.).

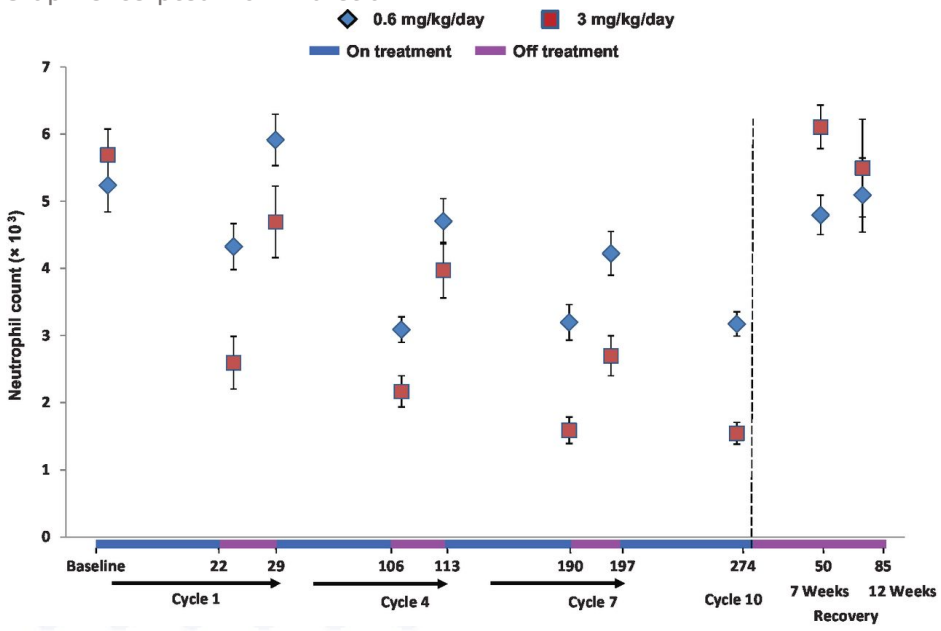
- In an analysis of mRNA expression levels in cell lines derived from localized HS, disseminated HS, systemic histiocytosis (SyH) and Langerhans cell histiocytosis (LCH) in dogs, the growth inhibitory effects of palbociclib were verified with the cell lines in vitro and in xenograft mouse model. Ingenuity pathway analysis suggested that the MAPK signaling pathway was activated in the localized HS and LCH cell lines. In vitro assessments revealed growth inhibitory effects of palbociclib, and a xenograft mouse model (using cell line from disseminated HS) exerted significant growth inhibitory effects (Hirabayashi et al.).

- Three of the four tested melanoma cell lines (LMCK, OLGA,CMM10; not CMM12) were sensitive to palbociclib (Bongiovanni et al.).

Safety/dosing

- In an in vivo study evaluating the toxicity of chronic palbociclib administration in dogs, 6 dogs/sex/group were administered palbociclib at 0, 0.6, or 3 mg/kg/day via oral gavage for 10 cycles, each consisting of 3 weeks of daily dosing and 1 week treatment-free. Blood samples for hematologic assessment (collected prior to the dosing phase, at the end of each dosing and treatment-free period [cycles 1, 4, 7], at the end of the dosing phase of cycle 10, and week 7 and 12 of the recovery period) revealed palbociclib-related decreases in all lineages (leukocytes, erythrocytes, and thrombocytes), with the greatest effect observed in neutrophils; and neutrophil counts partially returned to pretest levels at the end of each 1-week treatment-free period and completely recovered by day 50 of the recovery period. Bone marrow aspirates (collected at the end of cycle 10) revealed moderate decreased cellularity in 3 of 8 animals administered 3 mg/kg/day and involved all hematopoietic cell lineages; the bone marrow was normal for all dogs at day 85 of the recovery phase. Subsequent in vitro evaluation utilizing human bone marrow mononuclear cells demonstrated that palbociclib-induced bone marrow suppression occurred through cell-cycle arrest, with no apoptosis at clinically relevant concentrations, was not lineage-specific, and was reversible upon palbociclib withdrawal. In contrast, treatment with chemotherapeutic agents (paclitaxel and doxorubicin) resulted in DNA damage and apoptotic cell death (Hu et al.).

Graph excerpted from Hu et al.:



:: Efficacy

None currently

Pharmacokinetics

Excerpted from the FDA NDA 207103:

Table 15. The mean (±SD) PK parameters of PD 0332991 (copied from the Applicant's submission)

Route	Dose (mg/kg)	Cmax (ng/mL)	tmax (hr)	t½ (hr)	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL (mL/min/kg)	Vdss (L/kg)	F (%)
IV	1.0	--	--	10.8 ± 0.3	2330 ± 258	1860 ± 222	7.22 ± 0.85	6.2 ± 0.8	--
PO	20	664 ± 247	8.7 ± 3.1	20.7 ± 5.7	NR	17400 ± 6900	--	--	36.9±12.4[a]

NR = Not reported due to extrapolation >20% in 2 of 3 dogs.

[a] F was calculated based on AUC(0-48 hr) for PO data.

Sources

- Best Pet Rx+ (https://bestpetrx.com/): (as of August 26, 2021) Unavailable.

+Please check their website to confirm that they can serve your state.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of August 26, 2021) Unavailable.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of July 14, 2021) Available in dose range* of 1.1 mg to 8 mg capsules:

Dose 1.1 mg capsules, quantity 30, ~ $93.25.

Dose 8 mg capsules, quantity 30, ~$164.75.

**This dose range may not appear on your online portal. If so, please call Wedgewood Pharmacy (call center 877.357.6613) to prescribe this drug.*

Anecdotal Information from Veterinary Oncologists

"Starting dose has been 0.2 mg/kg/day."

"Could develop thrombocytopenia, which appears to have a delayed onset (several weeks after starting) and long-lasting (nadir a couple weeks after discontinuation, although improving thereafter). Otherwise, they are clinically fine." NB: for this patient, there was concurrent use of metronomic chlorambucil and concern for possible Anaplasmosis, both of which could have contributed to the thrombocytopenia.

References

Bongiovanni L et al. *H2AFZ*: A novel prognostic marker in canine melanoma and a predictive marker for resistance to CDK4/6 inhibitor treatment. *Front Vet Sci*. 2021 Aug 16;8:705359. doi: 10.3389/fvets.2021.705359.

Guscetti F et al. Molecular homology between canine spontaneous oral squamous cell carcinomas and human head-and-neck squamous cell carcinomas reveal disease drivers and therapeutic vulnerabilities. *Neoplasia*. 2020 Dec;22(12):778-788. doi: 10.1016/j.neo.2020.10.003.

Hirabayashi M et al. mRNA sequencing analysis and growth inhibitory effects fo palbociclib on cell lines from canine histiocytic proliferative disorders. *Vet Comp Oncol.* 2022 Mar 12. doi: 10.1111/co.12812.

Hu W et al. Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation from cytotoxic chemotherapies. *Clin Cancer Res*. 2016 Apr 15;22(8):2000-8. doi: 10.1158/1078-0432.CCR-15-1421.

Ibrance® (Palbociclib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 207103 (capsule), February 2015.

Ibrance® (Palbociclib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 212436 (tablet), November 2019.

Schoos et al. In vitro study to assess the efficacy of CDK4/6 inhibitor Palbociclib (PD-0332991) for treating canine mammary tumours. *Vet Comp Oncol*. 2019 Dec;17(4):507-521. doi: 10.1111/vco.12514.

Questions? Call Vidium Customer Support at (833) 794-0318, email VidiumInfo@tgen.org, or visit www.vidiumah.com

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