Olaparib

Lynparza®

Mechanism of Action

According to the FDA NDA 206162, olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor, first in its class to be approved by the FDA to treat patients with mutations in BRCA genes. It is clastogenic (causes breaks in chromosomes that result in the gain, loss, or rearrangements of chromosomal segments), and its mechanism of action involves an interaction with the enzymatic DNA repair machinery that carries out single-strand break detection and repair. So, the rationale for its use (at least for the clinical trials that were conducted to support NDA submission) was that combining the activity of olaparib with a deficiency in the double-strand DNA break repair pathway may lead to an enhanced accumulation of double-strand breaks leading to tumor cell death

Toxicology

According to the FDA NDA 206162:
In beagles given daily olaparib for **26 weeks** at **1, 3, and 10 mg/kg/day**, there were no test article-related clinical signs; there were no remarkable changes in clinical chemistry and urinalysis parameters; and there were no test article-related early mortalities. The major organ for toxicity was the hematopoietic system. Reduced circulating RBCs and leukocyte populations correlated with microscopic findings in the bone marrow, thymus, spleen, and liver. Dogs given ≥3 mg/kg/day had a reduction in red cell mass, reticulocytes, platelets, and leukocyte counts; minimal to slight inflammation was noted in the stomach and prostate gland; and there was no effect on liver function. Systemic exposure in week 13 and week 26 was comparable to day 1, which indicates no apparent accumulation of olaparib after repeat dosing.

In beagles given daily olaparib for **28 days** at **2, 5, and 15 mg/kg/day**, clinical signs and urinalysis were unremarkable; there were no test article-related effects on clinical chemistry, and all animals survived to scheduled necropsy. The major target organ was the hematopoietic system. Olaparib caused a dose-dependent decrease in reticulocytes, platelets, total leukocytes, and lymphocytes at ≥2.5 mg/kg/day, corresponding to microscopic findings of bone marrow atrophy and delays in erythroid cell development. Minimal or slight microscopic findings were also observed in the spleen, GI tract, kidneys, urinary bladder, parathyroid, and prostate, primarily at ≥5 mg/kg.

FDA Labeled Use

Lynparza® 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 492975):
Lynparza® is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for:

Ovarian cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
- in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Breast cancer

- for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Pancreatic cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Prostate cancer

- for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Selected Canine Publications

:: Preclinical

In both a canine mammary carcinoma cell line (CF4.1Mg) and a human breast adenocarcinoma cell line (MDA-MB-468), there was decrease in PARP-1 protein and gene expression after treatment with carboplatin, olaparib and both in combination compared to the group without treatment ($p<0.05$). Moreover, in both lines, reduction in invasion rate was observed after

treatment with carboplatin, olaparib and when combined, compared to the control group ($p<0.05$, Moschetta-Pinheiro et al.)

Safety/dosing

None currently

Efficacy

None currently

Pharmacokinetics

Excerpted from the FDA NDA 206162:

Table 34. Mean toxicokinetic parameters of oral olaparib administered to dogs daily for 26 weeks

	Sex	Dose (mg/kg)	T_{max} (h)	$T_{1/2}$ (h)	C_{max} (ng/ml)	C_{max}/D (ng/ml)/ (mg/kg)	$AUC_{(0\text{-}24h)}$ (h·ng/ml)	$AUC_{(0\text{-}24h)}/D$ (h·ng/ml)/ (mg/kg)
Day 1	Male	1	1.50	4.35	234	234	1470	1470
		3	1.38	4.06	559	186	3150	1050
		10	6.00	12.4	1500	150	20000	2000
	Female	1	1.50	7.47	167	167	1510	1510
		3	1.75	2.29	352	117	3030	1010
		10	2.00	4.23	1180	118	12400	1240
Week 13	Male	1	2.00	3.62	197	197	1660	1660
		3	2.50	5.30	376	125	3150	1050
		10	1.75	7.10	1070	107	14300	1430
	Female	1	1.25	8.40	188	188	1510	1510
		3	1.75	7.24	426	142	3130	1040
		10	2.00	3.68	1020	102	10800	1080
Week 26	Male	1	1.50	3.19	330	330	2180	2180
		3	1.25	3.96	597	199	3830	1280
		10	1.67	10.6	1540	154	15600	1560
	Female	1	1.00	3.82	248	248	1190	1190
		3	1.50	4.86	587	196	3600	1200
		10	4.25	4.22	1220	122	14000	1400

Sources

- Best Pet Rx+ (https://bestpetrx.com/contact-us/): (as of September 7, 2021) Available in many doses; prices vary by dose ranges:

  Dose range 0.01 mg to 50 mg capsules, quantity 30, ~$219.
  Dose range 50.1 mg - 100 mg capsules, quantity 30, ~$321.
  Dose range 100.1 mg - 150 mg capsules, quantity 30, ~$388.
  +Please check their website to confirm that they can serve your state.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of September 29, 2021) Unavailable.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/items/olaparib-capsule.html): (as of September 7, 2021) Available dose range* of 12 mg to 200 mg capsules:

  Dose 12 mg capsules, quantity 30, ~$98.
  Dose 200 mg capsules, quantity 30, ~$344.
  **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 of 2.5 – 3 mg/kg once daily. Very uncommon to have side effects, and no abnormalities noted on lab work"
"Combining with other cytotoxic chemotherapy (eg. carboplatin) or metronomic chlorambucil has been fine"
"Starting dose of 2 mg/kg BID (for 4 mg/kg/day), and planned dose escalation to 2.5 mg/kg BID (5 mg/kg/day)"
"Consider monthly CBC to screen for cytopenias."
"Consider periodic blood chemistry to screen for other organ dysfunction."

References

Lynparza® (Olaparib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 206162 (capsule), December 2014.

Lynparza® (Olaparib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 208558 (tablet), August 2017.

Moschetta-Pinheiro MG et al. Treatment of triple negative cell lines with olaparib to block DNA repair. *Anticancer Agents Med Chem.* 2021 Oct 7. doi: 10.2174/1871520621666211008104543.

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

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