

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

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

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. Olaparib capsules are indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated 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.

Olaparib tablets are indicated for ovarian cancer, breast cancer, pancreatic cancer, and prostate

cancer with deleterious or suspected deleterious germline or somatic BRCA mutation or homologous recombination repair gene mutation (these indications were updated May 2020 - please see package label for full indication details).

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 _(0-24h) (h·ng/ml)	AUC _(0-24h) /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.

- Stokes Pharmacy (<https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/>): (as of September 29, 2021), not currently available.

- 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.

Anecdotal Information from Veterinary Oncologists

"Dosing has been 2.5 – 3 mg/kg/day. Very uncommon to have side effects, and no abnormalities noted on lab work."

"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 206162Orig1s000), December 2014.

Disclaimer: Any information regarding therapy does not promise or guarantee that a particular drug or treatment regimen will be safe, effective, or helpful in the treatment of disease in any patient. The selection of any drug or drugs for patient treatment is done at the discretion of the treating veterinarian. Use caution when combining multiple drugs and be aware of potential drug interactions. Drug costs were provided by the respective pharmacies on the dates indicated, and drug costs and availability are subject to change at the discretion of the providing pharmacy. The treating veterinarian is encouraged to refer to drug labeling, published literature, and safety data for warnings, precautions, and dosing guidelines. Referenced articles, if any, were manually selected and do not necessarily reflect the entirety of literature on the drug or drugs. Vidium Animal Health®'s services, including but not limited to the information contained herein, are governed by Vidium's Terms & Conditions, which are available via email by requesting them at vidiuminfo@tgen.org.

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