DRUG NAME: Olaparib

SYNONYM(S): AZD-2281 [1], KU-0059436, KU-59436

COMMON TRADE NAME(S): LYNPARZA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Olaparib is a selective inhibitor of enzymes of the poly (ADP-ribose) polymerase family (e.g., PARP-1, PARP-2, and PARP-3). Binding to PARP inhibits single stranded DNA base excision repair and creates PARP-DNA complexes that lead to double-stranded DNA breaks, ultimately causing cell death in tumours that cannot repair double-stranded breaks reliably (e.g., tumours with homologous replication deficiency, such as those with BRCA1/2 mutation). [2] Olaparib is an immunosuppressive agent. [3]

PHARMACOKINETICS:

Oral Absorption	rapid oral absorption; peak plasma concentration 1-3 h after dosing	
Distribution	co-administration with food delays time to peak concentration by 2 h and increases the AUC by ~20%	
	cross blood brain barrier?	no (in animal studies)
	volume of distribution	167 L
	plasma protein binding	82%
Metabolism	extensively metabolized by CYP 3A4; many metabolites with unknown activity	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	fecal and urinary excretion of unchanged olaparib and metabolites	
	urine	44%
	feces	42%
	terminal half life	11.9 h
	clearance	8.64 L/h

Adapted from standard reference [3] unless specified otherwise.

USES:

Primary uses:

*Breast cancer
*Ovarian cancer
*Pancreatic cancer
*Prostate cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:

- ***pneumonitis***, including fatal cases, occurs rarely; patients with lung metastases, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy may be predisposed [3,4]
- recovery from prior ***hematologic toxicity*** should be confirmed before starting olaparib treatment [5]

Carcinogenicity: Formal studies have not been conducted. Cases of secondary myelodysplastic syndrome and acute myeloid leukemia have been reported, the majority of which were fatal. In patients who developed MDS/AML, the duration of therapy with olaparib widely varied from less than 6 months to greater than four years. Previous treatment with cisplatin or other DNA damaging treatments (including radiotherapy), history of previous cancer or bone marrow dysplasia, and germline BRCA mutations were considered potential contributing factors. [5]

Mutagenicity: Not mutagenic in Ames test. Olaparib is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. [3]

Fertility: No adverse effects on male or female fertility were observed in animal studies. [3,6]

Pregnancy: Fetal risk was demonstrated in animal studies at drug exposures less than the equivalent recommended human dose. Toxicities included embryofetal lethality, reduced early embryofetal survival, decreased fetal weight, as well as increased birth defects such as additional liver lobes, left-sided umbilical artery, dilated or kinked ureters, major eye abnormalities, and skeletal malformations. Women of childbearing potential should use effective contraception while on olaparib and for at least one month following the last dose. The efficacy of hormonal based contraceptives may be reduced due to potential olaparib CYP3A induction. It is unclear whether this interaction is clinically significant *in vivo*, therefore doctors may choose to recommend additional non-hormonal contraception. Consider pregnancy tests in women of child bearing potential prior to starting olaparib, periodically during treatment, and at one month post therapy. [3,7,6]

Breastfeeding is not recommended during therapy and for one month after the last dose due to potential secretion into breast milk. [3]

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] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. [9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (23-50%, severe 9-23%) [5]
	febrile neutropenia (<1%)
	leukopenia (7-25%, severe 1-5%) [5]
	lymphopenia (6-13%, severe 1-5%) [5]
	neutropenia (8-27%, severe 4-9%) [5]
	thrombocytopenia (4-16%, severe <6%) [5]
gastrointestinal	*emetogenic potential:* low to moderate [10-13]; refer to protocol by which patient is being treated
	abdominal pain (2-18%, severe 1%) [5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	constipation (28%) [5]
	diarrhea (17-38%, severe <3%) [5]
	dyspepsia (6-17%) [5]
	gastrointestinal reflux disease [5] (3%)
	nausea (28-77%, severe <4%) [5,14,15]
	stomatitis (3-13%, severe <2%) [5]
	vomiting (13-40%, severe <3%) [5]
general disorders and administration site conditions	***fatigue,*** including ***asthenia*** (37-67%, severe 2-7%) [5]
	fever (14%) [5]
hepatobiliary	hepatotoxicity [5]
immune system	angioedema [5] (<1%)
	hypersensitivity (1-2%, severe <1%) [5]
infections and infestations	cystitis [5] (2%)
	urinary tract infection (12%, severe 1%) [5]
investigations	creatinine increase (2-11%) [5]; returns to baseline after treatment, no clinical sequelae noted
	hemoglobin decrease (65-98%, severe 8-19%) [5]
metabolism and nutrition	appetite decrease (13-31%, severe <2%) [5]
neoplasms	***myelodysplastic syndrome/acute myeloid leukemia*** (1-4%) [14,15,5]; see paragraph following **Side Effects** table
nervous system	dizziness (7-20%, severe <1%) [5]
	dysgeusia (7-27%) [5]
	headache (6-26%, severe <1%) [5]
respiratory, thoracic and mediastinal	cough (9-21%, severe 1%) [5]
	dyspnea (4-16%, severe <2%) [5]
	pneumonitis (<1%) [5]; sometimes fatal
	pulmonary embolism [5] (1-7%)
skin and subcutaneous tissue	rash (5-18%, severe <1%) [5]
vascular	***venous thromboembolic event*** (1-3%, severe <2%) [5]

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Hematologic toxicities (e.g., grade 3 thrombocytopenia, anemia, neutropenia, and lymphopenia) have been reported and may occur early in treatment. Avoid using olaparib in combination with other myelosuppressive agents. In patients who have received prior myelosuppressive treatments, delay initiation of olaparib until blood counts have recovered. Interrupt olaparib treatment for severe hematological toxicity or blood transfusion dependence. If blood parameters are still abnormal after four weeks of treatment interruption, bone marrow analysis and/or blood cytogenetic analysis is recommended. Discontinue olaparib if myelodysplastic syndrome/acute myeloid leukemia is confirmed. [5]

Nausea and vomiting are generally reported early in treatment. First onset of nausea is usually reported within the first month of treatment and vomiting is usually reported within the first two months of treatment in affected patients. Most of these events are reported to improve over time without medical intervention while continuing olaparib. [5]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice [3]	may increase plasma level of olaparib	may inhibit CYP 3A4 metabolism of olaparib in the intestinal wall	avoid grapefruit and grapefruit juice
itraconazole [3,6]	olaparib C_{max} increased 1.42 fold, AUC increased 2.7 fold	strong inhibition of CYP3A metabolism by itraconazole	avoid concurrent use; if avoidance is not possible, reduce olaparib dose from 300 mg bid to 100 mg bid and monitor for toxicity
rifampin [3,6]	olaparib C_{max} decreased by 71%, AUC decreased by 87%	strong induction of CYP3A metabolism by rifampin	avoid concurrent use

Olaparib is predominately metabolized by CYP3A. Avoid concurrent use of strong and/or moderate CYP3A **inhibitors** if possible as these may increase olaparib plasma concentrations. If co-administration with a strong CYP3A inhibitor cannot be avoided, consider olaparib dose reduction from 300mg bid to 100 mg bid. If co-administration with a moderate CYP3A inhibitor cannot be avoided, consider olaparib dose reduction from 300 mg bid to 150 mg bid. [3,6] Avoid concurrent use of strong and/or moderate CYP3A **inducers** as the efficacy of olaparib may be decreased. [3]

Olaparib induces CYP 1A2, 2B6, and 3A4 mRNA. Olaparib also inhibits CYP 3A4 *in vitro*. Clinical significance is unknown. [3,6,16]

Olaparib is a substrate of P-gp and MDR1 and an inhibitor of BCRP, MDR1, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K *in vitro*; clinical significance is unknown. [3,6]

SUPPLY AND STORAGE:

Oral: AstraZeneca supplies olaparib as 100 mg and 150 mg tablets. Store at 2-30°C. Keep in original packaging to protect tablets from moisture (bottle contains desiccant). [17,18]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral [19-22]: ***300 mg*** (range 100-300 mg) ***PO twice daily***

Administer with food or on an empty stomach.

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure [23]:

Creatinine clearance (mL/min)	Dose
>50	no adjustment required
31-50	200 mg twice daily
≤30	no information found

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Calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L

* For males N=1.23; for females N=1.04

Dosage in hepatic failure [23]*:*

- mild or moderate impairment (Child-Pugh A or B): no adjustment required
- severe impairment (Child-Pugh C): no information found

Dosage in dialysis: no information found

***Children*:** no information found

REFERENCES:

1. Chase DM, Patel S, Shields K. Profile of olaparib in the treatment of advanced ovarian cancer. Int J Wom Health ; 2016;8:125–129
2. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Onc ; 2015;33(3):244–251
3. AstraZeneca Canada Inc. LYNPARZA® product monograph. Mississauga, Ontario; April 27, 2016.
4. Lexicomp Online®: (database on the Internet). Olaparib. Lexi-Comp Inc.; Accessed 18 Ma, 2016. Available at: http://online.lexi.com
5. AstraZeneca Canada Inc. LYNPARZA® product monograph. Mississauga, Ontario; May 22, 2024.
6. AstraZeneca Pharmaceuticals LP. LYNPARZA® product monograph. Wilmington, DE, USA; Decembe, 2014.
7. AHFS Drug Information® (database on the Internet). Olaparib. Lexi-Comp Inc.; Accessed 18 Ma, 2016. Available at: http://online.lexi.com
8. Anna Tinker MD. BC Cancer Agency Genitourinary Tumour Group. Personal communication. 31 Jul, 2016.
9. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med ; 2012;366:1382–1392
10. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 , 2022.
11. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. J Clinical Oncol ; 2020;38(24):2782–2797
12. Jordan K, Chan A, Gralla RJ, et al. Emetic risk classification and evaluation of the emetogenicity of antineoplastic agents - updated MASCC/ESMO consensus recommendation. 2024;32(53):1–7
13. National Comprehensive Cancer Network. www.nccn.org. NCCN Clinical Practice Guidelines in Oncology: Antiemesis V.1.2024. National Comprehensive Cancer Network, Inc.; Accessed April 18, 2024. Updated Dec 13, 2023. Available at: http://www.nccn.org
14. Ledermann JA, El-Khouly F. PARP inhibitors in ovarian cancer: clinical evidence for informed treatment decisions. Br J Cancer. ; 2015;113:S10–S16
15. Parkes EE, Kennedy RD. Clinical application of poly(ADP-ribose) polymerase inhibitors in high-grade serous ovarian cancer. Oncologist ; 2016;21:586–593
16. AstraZeneca UK. LYNPARZA® product monograph. Macclesfield, Cheshire, UK; December 16, 2014.
17. AstraZeneca Canada Inc. LYNPARZA® product monograph (tablets). Mississauga, Ontario; May 8, 2018.
18. AstraZeneca Canada Inc. Medical Information. Personal communication re: LYNPARZA® tablet stability. 3 Apri, 2019.
19. AstraZeneca Canada Inc. LYNPARZA® product monograph (tablets). Mississauga, Ontario; July 10, 2023.
20. BC Cancer Gynecology Tumour Group. (UGOOVOLAP) BC Cancer Protocol Summary for Treatment of Relapsed BRCA-mutated Platinum Sensitive Ovarian Cancer With Olaparib. Vancouver, British Columbia: BC Cancer; 1 Septembe , 2018.
21. BC Cancer Gynecologic Oncology Tumour Group. (UGOOVOLAPM) BC Cancer Protocol Summary for Maintenance Treatment of Relapsed, BRCA-mutated, Platinum Sensitive and Responsive Epithelial Ovarian Cancer With Olaparib. Vancouver, British Columbia: BC Cancer; 1 Septembe , 2018.
22. BC Cancer Breast Tumour Group. (UBRAJOLA) BC Cancer Protocol Summary for Treatment of BRCA-Mutated High-Risk Early Breast Cancer using Olaparib. Vancouver, British Columbia: BC Cancer; September 1 , 2023.
23. AstraZeneca Canada Inc. LYNPARZA® product monograph (tablets). Mississauga, Ontario; May 13, 2020.

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