Drug Monograph

A - Drug Name

olaparib

COMMON TRADE NAME(S): Lynparza®

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B - Mechanism of Action and Pharmacokinetics

Olaparib is a selective inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3) involved in DNA repair. Olaparib has been shown to inhibit the growth of solid tumours, especially those deficient in BRCA function (e.g., BRCA mutation-positive ovarian tumours).

Absorption	Olaparib is absorbed rapidly with peak concentration achieved 1.5 hours after a single dose.	
	Effects with food	Co-administration with food slowed the rate of absorption but did not significantly affect the extent of absorption
Distribution	PPB	82%
Metabolism	Olaparib is extensively metabolized in the liver by CYP3A isoenzymes. It is currently unknown whether metabolites are active.	
Elimination	Half-life	terminal elimination: approx. 15 hours
	Feces	42% in 7 days
	Urine	44% in 7 days

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C - Indications and Status

Health Canada Approvals:

- Ovarian cancer
- Breast cancer
- Prostate cancer
- Pancreatic cancer

Refer to the product monograph for a full list of approved indications and details.

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following adverse effects were reported in patients in the phase III trial comparing olaparib monotherapy to placebo in patients with ovarian, fallopian tube or primary peritoneal cancer who responded to first-line platinum-based chemotherapy. Severe adverse effects from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Venous thromboembolism (2%) (8% in mCRPC)	E
Dermatological	Rash (10%)	E
Gastrointestinal	Abdominal pain (18%)	E
	Anorexia (20%)	E
	Constipation (28%)	E
	Diarrhea (34%) (3% severe)	E
	Dyspepsia (17%)	E
	Mucositis (11%)	E

	Nausea, vomiting (77%) (1% severe)	I E
General	Fatigue (64%) (4% severe)	E
Hematological	Myelosuppression ± infection, bleeding (39%) (22% severe; including anemia)	E
Hepatobiliary	Hepatotoxicity (rare)	E
Hypersensitivity	Hypersensitivity (2%)	I
Neoplastic	Secondary malignancy (1%) (MDS, AML)	D L
Nervous System	Dizziness (20%)	E
	Dysgeusia (26%)	E
	Headache (23%)	E
Renal	Creatinine increased (8%)	E
Respiratory	Cough, dyspnea (18%)	E
	Pneumonitis (rare)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for olaparib include nausea, vomiting, fatigue, myelosuppression ± infection, bleeding, diarrhea, constipation, dysgeusia, headache, anorexia, dizziness and abdominal pain.

Nausea and vomiting were generally reported with early onsets, but most of these events improved over time without intervention.

Myelodysplastic syndrome (MDS) and/or Acute myeloid leukemia (AML) have been reported rarely and were fatal in most cases. Affected patients received olaparib for less than 6 months to over 4 years and had other contributing factors, including previous treatment with DNA damaging agents (radiation, platins, etc.). Most were in germline BRCA mutation carriers and some had a history of previous cancer or bone marrow dysplasia. In the SOLO2 study, patients with BRCAm platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum chemotherapy had a higher incidence (8%) of MDS/AML.

Severe **myelosuppression** has been reported, including hemorrhagic stroke associated with thrombocytopenia. Anemia is the most common severe adverse effect reported in clinical trials. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Pneumonitis, including fatal cases, have been reported rarely.

Cases of **drug-induced liver injury (DILI)** have been observed during post-marketing.

Venous thromboembolic events, including pulmonary embolism have been observed and had no consistent clinical pattern. A higher incidence was reported in patients with metastatic castration resistant prostate cancer who received olaparib with androgen deprivation therapy (ADT), compared with other indications. Monitoring is recommended and treatment may be necessary.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Various treatment indications require a validated test to determine BRCA or ATM mutation status. Refer to the product monograph for details.

In ovarian cancer, treatment should start no later than 8 weeks after completion of platinum-containing chemotherapy. (Refer to EAP for detailed funding criteria).

In metastatic castration-resistant prostate cancer (mCRPC), patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently, or should have had bilateral orchiectomy.

For adjuvant treatment of HER2-negative high risk early breast cancer, continue concurrent endocrine therapy in patients with hormone receptor positive breast cancer as per clinical guidelines. Start olaparib at least 2 weeks (no more than 12 weeks) after completion of the last treatment, including surgery, chemotherapy, or radiation therapy (Refer to CADTH recommendations).

Patients should have recovered from prior hematologic toxicities before starting olaparib (Hgb, ANC and platelets ≤ grade 1).

Adults:

Oral: 300 mg BID

Dosage with Toxicity:

Dose Level	Olaparib Dose
0	300 mg BID
-1	250 mg BID
-2	200 mg BID
-3	Discontinue

Toxicity	Severity	Action
Platelets or ANC	≥ Grade 3 or blood transfusion dependence	Hold up to 4 weeks* and monitor CBC. Then, may consider dose reduction.
Hemoglobin		Hold up to 4 weeks* and monitor CBC. Then, consider a dose reduction after severe anemia, to avoid multiple transfusions.
Signs and symptoms of pneumonitis	Any	Hold and investigate. If confirmed, discontinue and treat appropriately.
Hepatotoxicity	Any	Hold and investigate. Consider discontinuing if severe drug-induced liver injury and manage appropriately.
MDS, AML or other clonal disorders		Hold and investigate. If confirmed, discontinue and treat appropriately.
Other non-hematologic	Grade 3 or 4	Hold up to 4 weeks** Upon recovery, consider dose reduction.

*Hold until ≤ grade 1. If blood parameters remain abnormal after 4 weeks, bone marrow analysis and/or blood cytogenetic analysis are recommended.

**Hold until ≤ grade 1. If toxicity recurs, reduce an additional dose level. Discontinue if more than 2 dose reductions are required.

Dosage with Hepatic Impairment:

Hepatic Impairment	Olaparib Dose
Child-Pugh A or B	No dose adjustment required
Child-Pugh C	Not recommended (not studied)

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Olaparib Dose
> 50	No dose adjustment required
31-50	200 mg BID
≤ 30 or end stage renal disease	Not recommended (limited data)

Dosage in the elderly:

Dose adjustment is not required. There is limited data in patients aged 75 and older.

Children:

Safety and efficacy have not been established in pediatric patients.

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F - Administration Guidelines

- Olaparib can be taken with or without food.
- Tablets should be swallowed whole and not chewed, crushed, dissolved or divided.
- Avoid grapefruit, starfruit, pomegranate, Seville oranges, their juices or products during treatment.
- If a dose is missed, the next dose should be taken at the regular scheduled time. A double dose should not be taken to make up for forgotten tablets.
- Store between 2 to 30^{o}C in original packaging to protect from moisture.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Do not co-administer with other myelosuppressive agents.
- Use with caution in patients who have received prior DNA damaging agents. MDS and AML have been reported.
- Use with caution in patients with lung cancer or metastases to the lungs, underlying pulmonary disease, smoking history and/or previous chemotherapy and radiotherapy as these patients are at increased risk of pneumonitis
- Patients experiencing fatigue and dizziness should use caution when driving or operating machines.

Other Drug Properties:

- Carcinogenicity: Probable
  Carcinogenicity studies have not been performed; however, secondary hematologic malignancies have been reported.

Pregnancy and Lactation:

- Clastogenicity: Yes
- Fetotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Embryotoxicity: Documented in animals
- Pregnancy:
  - Olaparib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for **6 months** after the last dose. Consider an additional non-hormonal (e.g., barrier) method of contraception as it is uncertain whether olaparib reduces the effectiveness of hormonal contraceptives. For patients with hormone dependent cancer, consider two non-hormonal contraceptive methods.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for **3 months** after the last dose.
  - Patients should not donate sperm during therapy and for **3 months** after the last dose; it is unknown whether olaparib is found in seminal fluid.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **1 month** after the last dose.
- Fertility effects: Probable
  Documented in animal studies with female animals

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H - Interactions

Olaparib is primarily metabolized by CYP3A and is susceptible to inhibitors and inducers of this isoenzyme. Olaparib is a substrate and inhibitor of MDR1 and a weak inhibitor of BCRP.

The possibility of CYP2C9 induction by olaparib and reduced substrate exposure (including hormonal contraceptives) cannot be excluded. Consider an additional non-hormonal (e.g., barrier) method of contraception. For women with hormone dependent cancer, consider two non-hormonal contraceptive methods.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ olaparib concentration and/or efficacy	↑ metabolism of olaparib	Co-administration with strong and moderate CYP3A inducers is not recommended. There is potential for substantially decreased olaparib efficacy with strong inducers.
CYP3A inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, pomegranate or starfruit)	↑ olaparib concentration and/or toxicity	↓ metabolism of olaparib	Co-administration with strong and moderate CYP3A inhibitors is not recommended. If the combination cannot be avoided, the dose of olaparib should be reduced to 100 mg bid (strong) or 150 mg bid (moderate).
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate exposure	Olaparib is predicted to be a weak inhibitor of CYP3A4 in vitro	Caution and monitor closely, especially with narrow therapeutic window substrates.
CYP 2B6 substrates (i.e. bupropion,	↓ substrate exposure	Olaparib induces CYP2B6 in vitro	Caution and monitor closely

cyclophosphamide, selegiline)			
Substrates of hepatic uptake transporters OATP1B1, OCT1 (e.g. bosentan, repaglinide, statins, metformin)	↑ substrate exposure	Olaparib inhibits OATP1B1, OCT1 in vitro	Caution and monitor closely, especially in combination with statins.
Substrates of renal uptake transporters OCT2, OAT3, MATE1, MATE2K (e.g. furosemide, methotrexate, metformin, cisplatin)	↑ substrate exposure	Olaparib inhibits renal uptake transporters in vitro	Caution and monitor closely
Myelosuppressive anticancer agents	potentiation and prolongation of myelosuppression	Additive	Avoid combining with other myelosuppressive agents

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and monthly for the first 12 months, then periodically thereafter, and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Clinical toxicity assessment for nausea and other GI and respiratory effects, fatigue, anemia, MDS, infection, bleeding and venous thromboembolism	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- olaparib - For the maintenance treatment of BRCA-mutated, high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients, based on criteria
- olaparib - For the treatment of metastatic castration resistant prostate cancer (mCRPC), based on criteria
- olaparib - For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated, human epidermal growth factor receptor 2-negative high risk early breast cancer, based on criteria
- olaparib - In combination with abiraterone, and prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer (mCRPC), based on criteria

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K - References

CADTH reimbursement recommendation: Olaparib (adjuvant treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated, human epidermal growth factor receptor 2-negative high risk early breast cancer). March 2023.

De Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020 May 28;382(22):2091-2102.Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 2019 Jul 25;381(4):317-27.

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Product information: Lynparza (Olaparib). AstraZeneca AB. August 20, 2024.

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Tew WP, Lacchetti C, Ellis A, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol 2020 Oct 20;38(30):3468-93.

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December 2024 Updated Adverse effects, Dosing, and Pregnancy/lactation sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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