

Drug Monograph

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A - Drug Name

olaparib (capsule)

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 capsules are absorbed rapidly with peak concentration achieved 1 to 3 hours after a single dose. Co-administration with a high-fat meal slowed the rate of absorption and increased the extent of absorption (AUC increased by approx. 20%).	
	Bioavailability	unknown
Distribution	PPB	82%
Metabolism	Olaparib is extensively metabolised in the liver by CYP3A isoenzymes. It's currently unknown whether metabolites are active.	
Elimination	Half-life	terminal elimination: approx. 12 hours
	Feces	42%
	Urine	44%

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C - Indications and Status

Health Canada Approvals:

For the maintenance treatment of adult patients with platinum-sensitive, relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) to platinum-based chemotherapy. Platinum sensitivity is defined as disease progressing at least 6 months after completion of the platinum-based chemotherapy.

Note: Olaparib capsules are only supplied through a controlled distribution program due to the differences in dosing and bioavailability between formulations. Capsules are only available for existing patients already using this dosage form; patients should be enrolled in the AstraZeneca Oncology Patient Support Program to continue to receive capsules.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Not applicable

The following adverse effects were reported in $\geq 10\%$ of patients in the phase III trial comparing olaparib tablet monotherapy to placebo (where incidence was at least 2% or more compared to placebo) in patients with platinum-sensitive relapsed ovarian cancer. Severe adverse effects from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Gastrointestinal	Anorexia (22%)	E
	Diarrhea (33%)	E
	Dyspepsia (11%)	E
	Mucositis (10%)	E
	Nausea, vomiting (76%) (3% severe)	I E
General	Fatigue (66%)	E
Hematological	Myelosuppression \pm infection, bleeding (20%) (severe)	E

Hypersensitivity	Hypersensitivity (rare)	I
Neoplastic	Secondary malignancy (2%) (MDS, AML)	D L
Nervous System	Dizziness (13%)	E
	Dysgeusia (27%)	E
	Headache (25%)	E
Renal	Creatinine increased (44%)	E
Respiratory	Cough (18%)	E
	<u>Pneumonitis (rare)</u>	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.
 Dose-limiting side effects are underlined.

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

The overall safety profile of the capsule and tablet formulations are similar.

The most common side effects for olaparib include nausea, vomiting, fatigue, ↑ creatinine, diarrhea, dysgeusia, headache, ↓ appetite, myelosuppression ± infection and bleeding, cough and dizziness. The most common severe adverse event is anemia, which appears to be exposure-related.

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 are fatal in most cases. Affected patients received olaparib for less than 6 months to over 2 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.

Severe **myelosuppression** has been reported, including hemorrhagic stroke associated with thrombocytopenia. CBC should be monitored regularly for the first 12 months of treatment and periodically thereafter (see Monitoring section). Anemia has been reported in 40% and increased MCV in 82% of patients.

Pneumonitis, including fatal cases have been reported rarely. If a patient presents with new or worsening respiratory symptoms and/or radiological abnormality, olaparib should be held and pneumonitis should be investigated. If pneumonitis is confirmed, olaparib should be discontinued and the patient treated appropriately.

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E - Dosing

Refer to protocol by which patient is being treated. Patients should have confirmation of germline or somatic BRCA mutation status using a validated test before starting treatment.

Treatment should start no later than 8 weeks after completion of platinum-containing chemotherapy. Patients should have recovered from prior hematologic toxicities before starting olaparib (Hgb, ANC, platelets ≤ grade 1).

Adults:

NOTE: Risk of Medication Error: Olaparib capsules and tablets are **not interchangeable**.

Oral: 400 mg (8 x 50 mg CAPSULES) BID

until disease progression or unacceptable toxicity

Dosage with Toxicity:

NOTE: The dose modifications below are applicable to the **capsule formulation** only.

Dose level	Olaparib (CAPSULE) dose
0	400 mg BID
-1	200 mg BID
-2	100 mg BID
-3	discontinue

Toxicity	Severity	Action
Hematologic	≥ Grade 3 or blood transfusion dependence	Hold up to 4 weeks* and monitor CBC. Restart at the same dose level once resolved.

Pneumonitis	Any grade	Hold and investigate. If confirmed, discontinue and treat 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 \leq grade 1. If blood parameters remain abnormal after 4 weeks, bone marrow analysis and/or blood cytogenetic analysis are recommended.

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

Dosage with Hepatic Impairment:

Liver function	Olaparib (CAPSULE) dose
Child Pugh A	no change
Child Pugh B or C	not recommended (not studied)

Dosage with Renal Impairment:

Creatinine clearance (ml/min)	Olaparib (CAPSULE) dose
> 50	no change
31-50	300 mg bid
\leq 30 or end stage renal disease	not recommended (limited data)

Dosage in the elderly:

Although there is limited data in patients aged 65 and older, dosage adjustment is not required.

Children:

Safety and efficacy has not been established in pediatric patients.

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F - Administration Guidelines

Olaparib capsules and tablets are **not interchangeable**. Ensure the dosage and formulation are indicated clearly on the prescription.

Note: Olaparib capsules are only supplied through a controlled distribution program due to the differences in dosing and bioavailability between formulations. Capsules are only available for existing patients already using this dosage form; patients should be enrolled in the AstraZeneca Oncology Patient Support Program to continue to receive capsules.

- Olaparib capsules should be administered on an empty stomach (at least 1 hour after a meal) and patients should refrain from eating for up to 2 hours
- Capsules 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 capsules.
- Olaparib should be stored between 2 to 25°C

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Co-administration with other myelosuppressive agents.

Other Warnings/Precautions:

- Olaparib capsules and tablets are not interchangeable; specify formulation and dosing on each prescription to prevent medication error
- 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.

Other Drug Properties:

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

Pregnancy and Lactation:

- Genotoxicity: Yes
- Fetotoxicity: Yes
- Embryotoxicity: Yes
Olaparib is not recommended for use in pregnancy. Adequate contraception should be used by women of child-bearing potential during treatment, and for at least one month after the last dose.
Olaparib may reduce the effectiveness of hormonal contraceptives. Consider an alternative (e.g. barrier) method of contraception.
A pregnancy test should be performed on all pre-menopausal women prior to treatment, regularly during treatment and one month after receiving the last dose.
- Excretion into breast milk: Probable
Breastfeeding is not recommended during treatment and for one month after the last dose.
- Fertility effects: Documented in animals
- Teratogenicity: Yes

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H - Interactions

Olaparib is primarily metabolised by CYP3A and is susceptible to inhibitors and inducers of this isoenzyme. The drug is predicted to inhibit CYP3A4 and induce CYP2B6 and is an inhibitor of

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several transporter proteins (OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K). Olaparib is a substrate and inhibitor of MDR1 and a weak inhibitor of BCRP. When olaparib was co-administered with other myelosuppressive agents, potentiation and prolongation of myelosuppression was observed.

Co-administration with a high-fat meal slowed the rate of absorption and increased the extent of absorption (AUC increase of 20%).

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 capsules should be reduced to 150 mg bid (strong) or 200 mg bid (moderate).
CYP3A4 substrates (e.g. cyclosporine, pimozone, 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, cyclophosphamide, selegiline)	↓ substrate exposure	olaparib induces CYP2B6 in vitro	Caution and monitor closely

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and monthly for the first 12 months; periodically thereafter
Pregnancy test	Before starting treatment in all premenopausal women of child-bearing potential, regularly during treatment and one month after the last dose
Clinical toxicity assessment for nausea and other GI effects, fatigue, anemia, MDS, infection, bleeding and respiratory effects	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](#))

- Platinum-sensitive, relapsed, BRCA-mutated ovarian, fallopian tube, or primary peritoneal cancer, with specific criteria

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K - References

Lynparza (olaparib) product monograph. AstraZeneca Canada Inc. May 1, 2018.

Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* 2014 Jul;15(8):852-61.

Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017 Jul 25 (published online).

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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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