**DRUG NAME:** Olaparib

**SYNONYM(S):** AZD-2281, 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). Olaparib is an immunosuppressive agent.

**PHARMACOKINETICS:**

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

Adapted from standard reference unless specified otherwise.

**USES:**

**Primary uses:**

*Ovarian cancer

*Breast cancer

**Other uses:**

Prostate cancer

*Health Canada approved indication
SPECIAL PRECAUTIONS:

Caution:
- olaparib is available as both tablets and capsules; these dosage formulations are NOT interchangeable due to differences in dosing and bioavailability of each formulation.\(^5\)\(^7\)
- olaparib capsules are only supplied through a controlled distribution program for patients who are enrolled in the AstraZeneca Oncology Support Program.\(^6\)
- pneumonitis, including fatal cases, occurs rarely; patients with lung metastases, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy may be predisposed.\(^3\)\(^8\)

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 two 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.\(^3\)

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.\(^3\)\(^9\)

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.\(^3\)\(^9\)\(^10\)

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.\(^1\) When placebo-controlled trials are available, adverse events will generally be included if the incidence is >5% higher in the treatment group.\(^2\)

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood and lymphatic system/ febrile neutropenia (see paragraph following Side Effects table)</td>
<td>anemia (25-40%, severe 4-18%)(^3)(^8)</td>
</tr>
<tr>
<td></td>
<td>lymphopenia (28-56%, severe 8-17%)(^3)(^8)</td>
</tr>
<tr>
<td></td>
<td>febrile neutropenia (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>neutropenia (15-32%, severe 4-8%)(^3)</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia (6-30%, severe 3-6%) (^3)(^8)</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>emetogenic potential: low-moderate(^13)</td>
</tr>
<tr>
<td></td>
<td>abdominal distension (13%)</td>
</tr>
</tbody>
</table>

Clinically important side effects are in bold, italics.
<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
</table>
| **Clinically important side effects are in ** _**bold, italics**_ | **abdominal pain** (18-43%, severe 8%)<sup>3,8,9</sup>  
**constipation** (10-21%)<sup>3,8</sup>  
**diarrhea** (27-31%, severe 2%)<sup>3,8</sup>  
**dyspepsia** (18-25%)<sup>3,8</sup>  
**nausea** (62-71%, severe 5%)<sup>3,14,15</sup>  
**stomatitis** (1-10%)<sup>8</sup>  
**vomiting** (32-43%, severe 2%)<sup>3,8</sup> |
| **general disorders and administration site conditions** | **asthenia** (14%, severe 1%)  
**fatigue** (52-68%, severe 8%)<sup>3,8</sup>  
**fever** (1-10%)<sup>8</sup>  
**peripheral edema** (10-20%)<sup>8</sup> |
| **infections and infestations** | **nasopharyngitis** (15%)  
**sepsis** (<1%)<sup>3,8</sup>; has been fatal  
**upper respiratory tract infection** (13-43%)<sup>3,8</sup>  
**urinary tract infection** (10-19%)<sup>3,8</sup> |
| **investigations** | **creatinine increase** (26-44%)<sup>3,8</sup>; returns to baseline after treatment, no clinical sequelae noted  
**hemoglobin decrease** (85-90%, severe 8-15%)<sup>3,8</sup> |
| **metabolism and nutrition** | **appetite decrease** (21-25%)<sup>3,8</sup>  
**hyperglycemia** (1-10%)<sup>8</sup>  
**hypomagnesemia** (1-10%)<sup>8</sup> |
| **musculoskeletal and connective tissue** | **arthralgia** (18%, severe 1%)  
**back pain** (10-25%, severe 3%)<sup>3,8</sup>  
**myalgia** (22-25%)<sup>8</sup> |
| **neoplasms** | **myelodysplastic syndrome/acute myeloid leukemia** (<1-2%)<sup>14,15</sup> |
| **nervous system** | **dizziness** (10-19%)<sup>3,8</sup>  
**dysguesia** (10-21%)<sup>3,8</sup>  
**headache** (10-25%)<sup>3,8</sup>  
**hemorhagic stroke** (<1%); see paragraph following Side Effects table  
**peripheral neuropathy** (1-10%)<sup>8</sup> |
| **psychiatric** | **anxiety** (1-10%)<sup>8</sup>  
**depression** (1-10%)<sup>8</sup>  
**insomnia** (1-10%)<sup>8</sup> |
| **renal and urinary** | **dysuria** (1-10%)<sup>8</sup>  
**urinary incontinence** (1-10%)<sup>8</sup> |
| **respiratory, thoracic and mediastinal** | **cough** (10-21%)<sup>3,8</sup>  
**dyspnea** (10-19%, severe 2%)<sup>3,8</sup>  
**pneumonitis** (<1%)<sup>3,8</sup>; sometimes fatal |
| **skin and subcutaneous tissue** | **dry skin, including eczema** (1-10%)<sup>8</sup>  
**pruritis** (1-10%)<sup>8</sup>  
**rash** (10-25%)<sup>3,8</sup> |
| **vascular** | **hot flashes** (1-10%)<sup>8</sup> |
Clinically important side effects are in **bold, italics**.

<table>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>**Clinically important side effects are in <strong>bold, italics</strong></td>
</tr>
<tr>
<td>hypertension (1-10%)</td>
<td>thromboembolic event (1-10%)</td>
</tr>
</tbody>
</table>

Adapted from standard reference unless specified otherwise.

**Hematologic toxicities** (e.g., grade 3 thrombocytopenia, including associated hemorrhagic stroke, 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.

**INTERACTIONS:**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>grapefruit juice</td>
<td>may increase plasma level of olaparib</td>
<td>may inhibit CYP 3A4 metabolism of olaparib in the intestinal wall</td>
<td>avoid grapefruit and grapefruit juice</td>
</tr>
<tr>
<td>itraconazole</td>
<td>olaparib C&lt;sub&gt;max&lt;/sub&gt; increased 1.42 fold, AUC increased 2.7 fold</td>
<td>strong inhibition of CYP3A metabolism by itraconazole</td>
<td>avoid concurrent use; if avoidance is not possible, reduce the dose of olaparib &quot;tablets&quot; from 300 mg bid to 100 mg bid and monitor for adverse effects</td>
</tr>
<tr>
<td>rifampin</td>
<td>olaparib C&lt;sub&gt;max&lt;/sub&gt; decreased by 71%, AUC decreased by 87%</td>
<td>strong induction of CYP3A metabolism by rifampin</td>
<td>avoid concurrent use</td>
</tr>
</tbody>
</table>

*Olaparib is supplied as tablets AND capsules. These formulations are NOT interchangeable due to differences in dosing and bioavailability of each formulation. Specific dosage recommendations for each formulation should be followed. For recommended dosing adjustment using olaparib capsules, refer to product specific information from AstraZeneca.

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 for "tablet formulation." If co-administration with a moderate CYP3A inhibitor cannot be avoided, consider olaparib dose reduction from 300 mg bid to 150 mg bid for "tablet formulation." Avoid concurrent use of strong and/or moderate CYP3A inducers as the efficacy of olaparib may be decreased.

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

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.

**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).

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Developed: 1 October 2017
Revised: 1 July 2020
AstraZeneca supplies olaparib as 50 mg **capsules**. Refrigerate. Patients may store capsules at room temperature for up to 3 months if needed. (Olaparib capsules are only supplied through a *controlled distribution program* for patients who are enrolled in the AstraZeneca Oncology Support Program.)

**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**

<table>
<thead>
<tr>
<th>Oral (<em>tablets</em>)(^7,19):</th>
<th><strong>300 mg</strong> (range 100-300 mg) <strong>PO twice daily</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer with food or on an empty stomach.</td>
<td></td>
</tr>
</tbody>
</table>

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

**Dosage in renal failure** (*tablets*)\(^20\):

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>no adjustment required</td>
</tr>
<tr>
<td>31-50</td>
<td>200 mg twice daily</td>
</tr>
<tr>
<td>≤30</td>
<td>no information found</td>
</tr>
</tbody>
</table>

Calculated creatinine clearance = \(N^* \times (140 - \text{Age}) \times \text{weight in kg} / \text{Serum Creatinine in µmol/L}\)

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

**Dosage in hepatic failure** (*tablets*)\(^20\):

- 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

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**Children:** no information found

**REFERENCES:**