LYNPARZA® (olaparib) Fact Sheet

ABOUT LYNPARZA® (olaparib) TABLETS

- LYNPARZA (olaparib) tablets (300mg twice daily) were approved in August 2017 for use as a maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy, regardless of *BRCA* status[1,2]
    - Maintenance treatment for recurrent ovarian cancer patients can be an important step in the treatment journey by slowing cancer growth and prolonging a response to chemotherapy[3]
- LYNPARZA tablets are also indicated (conversion from the current accelerated approval[4]) for use in adult patients with deleterious or suspected deleterious germline *BRCA* (*gBRCA)*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy; patients for this indication are selected for therapy based on an FDA-approved companion diagnostic[1]
    - LYNPARZA tablets (2 tablets twice daily) are now available for this indication as opposed to capsules (8 capsules twice daily)[1,5]

ABOUT LYNPARZA CAPSULES

- LYNPARZA was first approved under the FDA's Accelerated Approval program in December 2014, as a capsule formulation, making it the first FDA-approved poly ADP-ribose polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious *gBRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer, who have been treated with three or more prior lines of chemotherapy[1,5,6]
- Since the US FDA approval in 2014, more than 3,000 advanced ovarian cancer patients have been treated with LYNPARZA[7]
    - LYNPARZA capsules (400mg twice daily) are still approved in the US as a monotherapy in patients with deleterious or suspected deleterious *gBRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.[5] LYNPARZA capsules will be available through a limited specialty pharmacy network and will continue to be available for patients who are currently being treated with the capsule formulation
- LYNPARZA may cause serious side effects that can lead to death, including bone marrow problems called myelodysplastic syndrome (MDS) or Acute Myeloid Leukemia (AML). Some people who have ovarian cancer and who have received previous treatment with chemotherapy, radiotherapy or certain other medicines for their cancer have developed MDS or AML during treatment with LYNPARZA. Symptoms of low blood cell counts are common during treatment with LYNPARZA, but can be a sign of serious bone marrow problems, including MDS or AML[1]

ABOUT PARP INHIBITORS

- LYNPARZA is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair[1]
    - *In vitro* studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death[1]
    - LYNPARZA was the first FDA-approved PARP inhibitor[6]
    - LYNPARZA may exploit tumor DNA damage response (DDR) pathway deficiencies to potentially kill cancer cells[6,8,9]
        - *The exact mechanism of action of LYNPARZA remains a subject of research

LYNPARZA CLINICAL TRIAL PROGRAM

- **Phase III SOLO-2 Trial**: LYNPARZA tablets demonstrated a significant improvement in progression-free survival (PFS) in g*BRCA*, platinum-sensitive, relapsed epithelial ovarian cancer patients compared with placebo in the maintenance setting[1,10]
    - LYNPARZA reduced the risk of disease progression or death by 70% (HR 0.30 [95% CI, 0.22-0.41], P<0.0001), with an investigator-assessed median PFS of 19.1 vs 5.5 months, compared with placebo[1]
    - In the LYNPARZA arm, the most common adverse events reported in 20% or more of patients across the SOLO-2 trial were nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection (URI)/influenza (36%), diarrhea (33%), arthralgia/myalgia (30%), dysgeusia (27%), headache (26%), decreased appetite (22%), and stomatitis (20%).[1] Most common

laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA in the maintenance setting (SOLO-2) were: increase in mean corpuscular volume (89%), decrease in hemoglobin (83%), decrease in leukocytes (69%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), increase in serum creatinine (44%), and decrease in platelets (42%)[1]

- **Phase II Study 19 Trial**: LYNPARZA capsules (400mg twice daily) demonstrated a statistically significant improvement in PFS in platinum-sensitive relapsed ovarian cancer patients treated in the maintenance setting.[2] LYNPARZA capsules are not indicated for maintenance therapy
    - Regardless of *BRCA* status, LYNPARZA reduced the risk of disease progression or death by 65% (HR 0.35 [95% CI, 0.25-0.49], P<0.0001), and had a median PFS of 8.4 vs 4.8 months compared with placebo[1]
    - Patients in Study 19, treated with LYNPARZA as a maintenance therapy, had a median overall survival of 29.8 months vs 27.8 months with placebo (HR 0.73 [95% CI, 0.55-0.95]) without adjusting for multiplicity[1]
    - In the LYNPARZA arm, the most common adverse events reported in 20% or more of patients across the Study 19 trial were nausea (71%), fatigue (including asthenia) (63%), vomiting (35%), diarrhea (28%), anemia (23%), respiratory tract infection (22%), constipation (22%), headache (21%), and decreased appetite (21%).[1] Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA in the maintenance setting (Study 19) were: increase in mean corpuscular volume (82%), decrease in hemoglobin (82%), decrease in leukocytes (58%), decrease in lymphocytes (52%), decrease in absolute neutrophil count (47%), increase in serum creatinine (45%), and decrease in platelets (36%)[1]

ABOUT OVARIAN CANCER

- Approximately 20,000 women in the US are diagnosed with ovarian cancer each year[11]
- Among US women, ovarian cancer is the ninth most common cancer and the fifth leading cause of cancer death[11]

IMPORTANT SAFETY INFORMATION FOR LYNPARZA TABLETS

DOSING AND ADMINISTRATION

To avoid substitution errors and overdose, **do not substitute LYNPARZA tablets with LYNPARZA capsules** on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Recommended tablet dose is 300 mg, taken orally twice daily, with or without food. Continue treatment until disease progression or unacceptable toxicity. For adverse reactions, consider dose interruption or dose reduction.

WARNINGS AND PRECAUTIONS

There are no contraindications for LYNPARZA.

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The duration of therapy in patients who developed secondary MDS/AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy, and some of these patients also had a history of previous cancer or bone marrow dysplasia.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in <1% of patients exposed to LYNPARZA, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt treatment with LYNPARZA and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving the final dose.

ADVERSE REACTIONS—MAINTENANCE SETTING

Most common adverse reactions (Grades 1-4) in ≥20% of patients in clinical trials of LYNPARZA in the **maintenance setting** for **SOLO-2**: nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection (URI)/influenza (36%), diarrhea (33%), arthralgia/myalgia (30%), dysgeusia (27%), headache (26%), decreased appetite (22%), and stomatitis (20%).

Study 19: nausea (71%), fatigue (including asthenia) (63%), vomiting (35%), diarrhea (28%), anemia (23%), respiratory tract infection (22%), constipation (22%), headache (21%), and decreased appetite (21%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA in the **maintenance setting (SOLO-2/Study 19**) were: increase in mean corpuscular volume (89%/82%), decrease in hemoglobin (83%/82%), decrease in leukocytes (69%/58%), decrease in lymphocytes (67%/52%), decrease in absolute neutrophil count (51%/47%), increase in serum creatinine (44%/45%), and decrease in platelets (42%/36%).

ADVERSE REACTIONS—ADVANCED g*BRCA*m OVARIAN CANCER

Most common adverse reactions (Grades 1-4) in ≥20% of patients in clinical trials of LYNPARZA for **advanced g*BRCA*m ovarian cancer after 3 or more lines of chemotherapy** (pooled from 6 studies) were: fatigue (including asthenia) (66%), nausea (64%), vomiting (43%), anemia (34%), diarrhea (31%), nasopharyngitis/upper respiratory tract infection (URI) (26%), dyspepsia (25%), myalgia (22%), decreased appetite (22%), and arthralgia/musculoskeletal pain (21%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for **advanced g*BRCA*m ovarian cancer after 3 or more lines of chemotherapy** (pooled from 6 studies) were: decrease in hemoglobin (90%), increase in mean corpuscular volume (57%), decrease in lymphocytes (56%), increase in serum creatinine (30%), decrease in platelets (30%), and decrease in absolute neutrophil count (25%).

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA in combination with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid concomitant use of strong or moderate CYP3A inhibitors. If a strong or moderate CYP3A inhibitor must be co-administered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid concomitant use of strong or moderate CYP3A inducers when using LYNPARZA. If a moderate inducer cannot be avoided, be aware of a potential for decreased efficacy of LYNPARZA.

USE IN SPECIFIC POPULATIONS

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Lactation: No data are available regarding the presence of olaparib in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild hepatic impairment (Child-Pugh classification A). There are no data in patients with moderate or severe hepatic impairment.

Renal Impairment: No adjustment to the starting dose is necessary in patients with mild renal impairment (CLcr 51-80 mL/min). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Please see Complete Prescribing Information (including Medication Guide) for LYNPARZA capsules and for LYNPARZA tablets

ABOUT ASTRAZENECA

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of diseases in three main therapy areas - Oncology, Cardiovascular & Metabolic Diseases and Respiratory. The Company also is selectively active in the areas of Autoimmunity, Neuroscience and Infection. AstraZeneca operates in over 100 countries and its innovative medicines are

used by millions of patients worldwide. For more information, please visit www.astrazeneca-us.com and follow us on Twitter @AstraZenecaUS.

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US-10435 Last Updated 8/17

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