LYNPARZA® (olaparib) Approved in Japan for BRCA-Mutated Metastatic Breast Cancer

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LYNPARZA is the First and Only PARP Inhibitor Approved for Use Beyond Ovarian Cancer

Second Approval in Japan for AstraZeneca and Merck’s LYNPARZA

KENILWORTH, N.J.--(BUSINESS WIRE)--AstraZeneca and Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) has approved LYNPARZA® (olaparib) tablets for use in patients with unresectable or recurrent BRCA-mutated (BRCAm), human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have received prior chemotherapy. Patients are selected for therapy based on an approved companion diagnostic.

Dave Fredrickson, executive vice president, head of the oncology business unit at AstraZeneca, said, “Earlier this year, LYNPARZA became the first PARP inhibitor available in Japan for advanced ovarian cancer. Now patients in Japan with BRCA-mutated, metastatic breast cancer will also have the opportunity to benefit from LYNPARZA. This latest approval underlines our ongoing efforts to make LYNPARZA available across multiple cancers as quickly as possible to patients around the world.”

Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories, said, “Metastatic breast cancer is a complex disease with remaining unmet medical need. This approval is significant for breast cancer patients as the evaluation of BRCA mutations, in addition to hormone receptor and HER2 status, now becomes an important step in the management of the disease.”

The approval is based on data from a randomized, open-label, Phase 3 OlympiaAD trial, which tested LYNPARZA versus chemotherapy. Patients were selected for therapy based upon a confirmed BRCA mutation. In the trial, LYNPARZA significantly prolonged progression-free survival (PFS) compared with chemotherapy, reducing the risk of disease progression or death by 42 percent (HR=0.58 [95% CI, 0.43-0.80]; p=0.0009). Median PFS was 7.0 months with LYNPARZA versus 4.2 months with chemotherapy.

LYNPARZA was generally well tolerated, with the majority of adverse events (AEs) reported as mild to moderate with a lower rate of Grade ≥3 AEs compared with chemotherapy (36.6% vs 50.5%). The most common AEs were nausea (50.2%), anemia (32.2%) and fatigue (22.4%).

LYNPARZA is also approved in Japan as maintenance treatment for women with platinum-sensitive relapsed ovarian cancer, regardless of BRCA mutation status. In Japan, the co-promotion of LYNPARZA by both companies began on July 1, 2018.

Important Safety Information

Contraindications
There are no contraindications for LYNPARZA.

Warnings and Precautions

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 also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy
(≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count 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 LYNPARZA treatment 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.

**Females**

Advertise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

**Males**

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

**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%/49%), and decrease in platelets (42%/36%).

**Adverse Reactions—Advanced gBRCAm Ovarian Cancer**

Most common adverse reactions (Grades 1-4) in ≥20% of patients in clinical trials of LYNPARZA for advanced gBRCAm 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 gBRCAm ovarian cancer (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%).

**Adverse Reactions—gBRCAm, HER2-Negative Breast Cancer**

Most common adverse reactions (Grades 1-4) in ≥20% of patients in OlympiAD were: nausea (58%), anemia (40%), fatigue (including asthenia) (37%), vomiting (30%), neutropenia (27%), respiratory tract infection (27%), leukopenia (25%), diarrhea (21%), and headache (20%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in OlympiAD were: decrease in hemoglobin (82%), decrease in lymphocytes (73%), decrease in leukocytes (71%), increase in mean corpuscular volume (71%), decrease in absolute neutrophil count (46%), and decrease in platelets (33%).

**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, there is a potential for decreased efficacy of LYNPARZA.

**Use In Specific Populations**

**Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on

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**Use In Specific Populations**

**Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or 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.

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

**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).

**Indications**

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

- For the treatment of adult patients with deleterious or suspected deleterious germline BRCA1-mutated (gBRCA1) or BRCA2 (gBRCA2) mutations, which are confirmed or suspected to be deleterious.

In patients with deleterious or suspected deleterious gBRCA1m, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

**Please see complete Prescribing Information, including Patient Information (Medication Guide).**

**About OlympiAD**

OlympiAD was a randomized, open-label, multi-center Phase 3 trial assessing the efficacy and safety of LYNPARZA tablets (300 mg twice daily) compared to physician’s choice of chemotherapy (capcitabine, eribulin, or vinorelbine) in 320 patients with human epithelial growth factor receptor 2 (HER2) negative metastatic breast cancer with germline BRCA1 (gBRCA1) or BRCA2 (gBRCA2) mutations, which are confirmed or suspected to be deleterious. The international trial was conducted in 19 countries across Europe, Asia, North America and South America.

Patients in the OlympiAD trial had HER2-negative gBRCA1- or gBRCA2-mutated breast cancer, which was hormone receptor positive (HR+) or triple negative, and received LYNPARZA for metastatic disease. Approximately half of the patients in the LYNPARZA and chemotherapy arm of the trial were HR+ (n=152) and approximately half were triple negative (n=150). Among the 205 patients treated with LYNPARZA, the median age was 44 years (range, 22 to 76). Before enrollment, patients had prior treatment with an anthracycline (unless contraindicated) and a taxane chemotherapy either in the neoadjuvant, adjuvant or metastatic setting, and no more than two prior lines of chemotherapy for metastatic disease. HR+ patients had received at least one endocrine medicine or were not eligible for endocrine medicines. Prior treatments with endocrine medicines were not counted as prior lines of chemotherapy.

The primary endpoint of the trial was progression-free survival (PFS) as measured by a Blinded Independent Central Review. Secondary endpoints included overall survival (OS), time to second progression or death (PFS2), objective response rate (ORR) and effect on health-related quality of life.

**About BRCA Mutations**

BRCA1 and BRCA2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role in maintaining the genetic stability of cells. When either of these genes is mutated, or altered, such that its protein product either is not made or does not function correctly, DNA damage may not be repaired properly and cells become unstable. As a result, cancers are more likely to develop additional genetic alterations that can lead to cancer.

**About Breast Cancer in Japan**

In Japan, breast cancer is the fifth leading cause of death among women. In Japanese women, breast cancer incidence peaks in the late forties, whereas in the U.S. and Europe, the peak incidence is in women over 60 years of age. Despite more treatment options becoming available during the past three decades, there is currently no cure for patients diagnosed with metastatic (Stage 4) breast cancer. In Japan, five- and 10-year relative survival rates for patients with Stage 4 breast cancer are as low as 32.6 percent and 15.6 percent, respectively. Therefore, the primary aim of treatment is to slow progression of the disease for as long as possible and improve or maintain a patient’s quality of life.

**About LYNPARZA ® (olaparib) 100 mg tablets**

LYNPARZA is the first-in-class PARP inhibitor and the first targeted treatment to potentially exploit DNA damage response (DDR) pathway deficiencies, such as BRCA mutations, to preferentially kill cancer cells. Specifically, in vitro studies have shown that LYNPARZA-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death. LYNPARZA is being tested in a range of DDR-deficient tumor types.

LYNPARZA, which is being jointly developed and commercialized by AstraZeneca and Merck, is approved for advanced ovarian cancer and metastatic breast cancer and has been used in over 20,000 patients worldwide. LYNPARZA has a broad and advanced clinical trial development program and AstraZeneca and Merck are working together to deliver it as quickly as possible to more patients across multiple cancer types.
About the AstraZeneca and Merck Strategic Oncology Collaboration

In July 2017, AstraZeneca and Merck, known as MSD outside the United States and Canada, announced a global strategic oncology collaboration to co-develop and co-commercialize LYNPARZA, the world’s first PARP inhibitor, and potential new medicine selumetinib, a MEK inhibitor, for multiple cancer types. Working together, the companies will develop LYNPARZA and selumetinib in combination with other potential new medicines and as monotherapies. Independently, the companies will develop LYNPARZA and selumetinib in combination with their respective PD-L1 and PD-1 medicines.

Merck’s Focus on Cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment.

As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers.

For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer’s disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s 2017 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

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