אפריל 2021

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

פרסום עדכון בעלון לרופא ובעלון לצרכן של התכשיר: Lynparza 100mg, 150mg

הרכב:

Olaparib 100mg
Olaparib 150mg

התוויות מאושרות:

Ovarian cancer
Lynparza is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*- mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
Lynparza is indicated in patients with deleterious or suspected deleterious *gBRCAm*, HER2-negative metastatic breast cancer who have 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 therapy.

First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma
Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

First-line Maintenance Treatment of Advanced Ovarian Cancer in Combination with Bevacizumab
Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:

- a deleterious or suspected deleterious BRCA mutation, and/or
- genomic instability

BRCA1/2 or ATM- Gene-mutated Metastatic Castration-Resistant Prostate Cancer
Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA1/2 or ATM- mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.

העדכונים המהותיים בעלון לרופא הם:

4.4 Special warnings and precautions for use

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Myelodysplastic syndrome/Acute myeloid leukaemia

The overall incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with Lynparza monotherapy, including long-term survival follow-up, was <1.5%, with higher incidence in patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see section 4.8). The majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >~~2~~ 4 years. ~~; data with longer durations of exposure are limited. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA*1/2) mutation carriers. The incidence of MDS/AML cases was similar among gBRCA1m and gBRCA2m patients (1.7% and 1.4%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia.~~ If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/ AML is confirmed, Lynparza should be discontinued and the patient treated appropriately.

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4.8 Undesirable effects

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When Lynparza is used in combination with bevacizumab the safety profile is generally consistent with that of the individual therapies.

Adverse events led to dose interruption and/ or reduction of olaparib in 57.4% of patients when used in combination with bevacizumab and led to permanent discontinuation of treatment with olaparib/bevacizumab and placebo/bevacizumab in 20.4% and 5.6% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (20.6%) and nausea (7.5%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.6%), nausea (3.4%) and fatigue/asthenia (1.5%).

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	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Uncommon** Myelodysplastic syndrome/ Acute myeloid leukaemia	**Uncommon** Myelodysplastic syndrome/ Acute myeloid leukaemia
Blood and lymphatic system disorders	**Very common** Anaemia[a] Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Common** Lymphopenia[a]	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia[a]
Immune system disorders	**Uncommon** Hypersensitivity[a], Angioedema[*]	- Rare Hypersensitivity[a]
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia	**Uncommon** Dizziness, Headache

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a], Dyspnoea[a]	**Common** Dyspnoea[a] **Uncommon** Cough[a]
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia **Common** Stomatitis[a], Upper abdominal pain	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis[a], Upper abdominal pain **Rare** Dyspepsia
Skin and subcutaneous tissue disorders	**Common** Rash[a] **Uncommon** Dermatitis[a] **Rare** Erythema nodosum	**Uncommon** Rash[a]
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Common** Blood creatinine increased **Uncommon** Mean cell volume increased	**Uncommon** Blood creatinine increased

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell count decreased; Neutropenia includes PTs of agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased; Thrombocytopenia includes PTs of platelet count decreased, platelet production decreased,plateletcrit decreased and thrombocytopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte count decreased; Cough includes PTs of cough and productive cough; Hypersensitivityincludes PTs of drug hypersensitivity and hypersensitivity; Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative.

* As observed in post-marketing setting

Description of selected adverse reactions

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Myelodysplastic syndrome/Acute myeloid leukaemia

MDS/AML are serious adverse reactions that occurred uncommonly in monotherapy clinical studies at the therapeutic dose, across all indications (0.4%). The incidence was 0.5% including events reported during the long term safety follow up (rate calculated based on overall safety population of 16108 patients exposed to at least one dose of oral olaparib in clinical studies). All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority

*of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA*1/2) mutation carriers. The incidence of MDS/AML cases was similar among gBRCA1m and gBRCA2m patients (2.3% and 1.6%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia.*

In patients with BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8.2% in patients receiving olaparib and 4% in patients receiving placebo at a follow-up of 5 years. In the olaparib arm, 9 out of 16 MDS/AML cases occurred after discontinuation of olaparib during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the olaparib arm and late onset of MDS/AML. The risk of MDS/AML remains < 1.5% at 5 year follow up in the first-line setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years (1.2% in SOLO1 study and 0.7% in PAOLA-1 study). For risk mitigation and management, see section 4.4.*

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5.1 Pharmacodynamic properties

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Detection of *BRCA1/2* mutations

Genetic testing should be conducted by an experienced laboratory using a validated test. Local or central testing of blood and/or tumour samples for germline and/or somatic *BRCA1/2* mutations have been used in different studies. DNA obtained from a tissue or blood sample has been tested in most of the studies, with testing of ctDNA being used for exploratory purposes. Depending on the test used and the international classification consensus, the BRCA1/2 mutations have been classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Homologous recombination deficiency (HRD) positive status can be defined by detection of a BRCA1/2 mutation classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Detection of these mutations could be combined with positive HRD score (below) to determine HRD positive status.

Detection of genomic instability

HR deficiency-associated genomic alterations that have been investigated in Paola-1 include genome-wide loss of heterozygosity, telomeric allelic imbalance and large scale transition, which are continuous measures with pre-defined criteria and score. Composite genomic instability score (GIS, also called HRD score) is determined when the combined measures and respective scores are used to assess the extent of specific genomic aberrations accumulated in tumour cells. Lower score defines lower likelihood of HR deficiency of tumour cells and higher score determines higher likelihood of HR deficiency of tumour cells at the time of the sample collection relative to exposure to DNA damaging agents. Validated cut-offs should be used to determine GIS positive status.

HRD positive status can be defined by a composite GIS score for HR deficiency-associated genomic alterations tested by an experienced laboratory using a validated test.

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At the final analysis of OS (61% maturity) the HR was 0.74 (95% CI 0.54-1.00; p=0.0537; median 51.7 months for olaparib vs 38.8 months for placebo) which did not reach statistical significance.The secondary endpoints TFST and PFS2 demonstrated a persistent and statistically significant improvement for olaparib compared with placebo. Results for OS, TFST and PFS2 are presented in Table 4 and Figure 4.

Table 4 Summary of key secondary objective outcomes for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	Placebo
OS (61% maturity)		
Number of events: Total number of patients (%)	116:196 (59)	65:99 (66)
Median time (95% CI), months	51.7 (41.5, 59.1)	38.8 (31.4, 48.6)
HR (95% CI) [a]	0.74 (0.54-1.00)	
P value (2-sided)	p=0.0537	
TFST (71% maturity)		
Number of events: Total number of patients (%)	139:196 (71)	86:99 (87)
Median time (months) (95% CI)	27.4 (22.6-31.1)	7.2 (6.3-8.5)
HR (95% CI) [a]	0.37 (0.28-0.48)	
P value* (2-sided)	P<0.0001	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months) (95% CI)	NR (24.1-NR)	18.4 (15.4-22.8)
HR (95% CI) [a]	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	

* Not controlled for multiplicity

[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazard model including response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy as covariates.

bd Twice daily; NR not reached; CI confidence interval; PFS2 time from randomisation to second progression or death; TFST Time from randomisation to start of first subsequent therapy or death.

<u>העדכונים המהותיים בעלון לצרכן הם:</u>

4. <u>תופעות לוואי</u>

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תופעות לוואי שכיחות מאוד (משפיעות על יותר מ- 1 מתוך 10 מטופלים):

- תחושת קוצר נשימה, תחושת עייפות מאוד גדולה, חיוורון או דופק מהיר - אלו יכולים להיות תסמינים של ספירה נמוכה של תאי דם אדומים (אנמיה).

תופעות לוואי שאינן שכיחות (משפיעות על עד 1 מתוך 100 מטופלים):

- תגובות אלרגיות (לדוגמה: נפיחות של הפנים, השפתיים, הלשון או הגרון, חרלת, קשיי נשימה או בליעה, סחרחורות העלולים להוות סימנים ותסמינים של תגובת רגישות יתר).
- בעיות חמורות במח העצם (תסמונת מיאלודיספלסטית (MDS) או לויקמיה מיאלואידית חריפה (AML)). אנא ראה סעיף 2.

מקרא לעדכונים המסומנים

הוספת טקסט מהותי מסומנת בצבע צהוב. מחיקת טקסט מסומנת בקו חוצה

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,

שרית רוזן - רוקחת ממונה

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