מאי 2022

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

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

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:

4.8 Undesirable effects

Summary of the safety profile

Lynparza has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥ 10%) were nausea, fatigue, anaemia, vomiting, diarrhoea, decreased appetite, headache, dysgeusia, cough, neutropenia, dyspnoea, dizziness, dyspepsia, leukopenia and thrombocytopenia.

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (16%), neutropenia (5%), fatigue/asthenia (5%), ~~leukopenia (3%) and~~ thrombocytopenia (3%) and leukopenia (2%).

Adverse reactions that most commonly led to dose interruptions and/or reductions in monotherapy were anaemia (~~16.7~~17%), fatigue/asthenia (6 %) , vomiting (6~~.3~~%), nausea (6~~.2~~%), ~~fatigue/asthenia (6.1 %)~~ and neutropenia (6~~.0~~%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.~~7~~8%), thrombocytopenia (0.8%), fatigue/asthenia (0.7%), nausea (0.66%), neutropenia (0.5%) and vomiting (0.5%).

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~~21.5%) and nausea (~~7.5~~9.5%) and fatigue/asthenia (5.2%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.6%), nausea (3.4%) and fatigue/asthenia (1.5%).

Tabulated list of adverse reactions

The safety profile is based on pooled data from ~~2091~~ 3077 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose.

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Table 1 Tabulated list of adverse reactions:

	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

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia[a]	**Uncommon** Dizziness, Headache
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	**Rare** ~~**Uncommon**~~ Blood creatinine increased

[a] MDS/AML ~~Anaemia~~ includes preferred terms (PTs) of acute myeloid leukaemia, myelodysplastic syndrome and myeloid leukaemia.

~~a~~Anaemia includes PTs of~~:~~ 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,~~ and lymphopenia ~~and T lymphocyte count decreased; Cough includes PTs of cough and productive cough.;~~

Hypersensitivityincludes PTs of drug hypersensitivity and hypersensitivity; Dysgeusia includes PTs of dysgeusia and taste disorder.

Cough includes PTs of cough and productive cough.

Dyspnoea includes PTs of dyspnoea and dyspnoea exertional;

Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.~~;~~

Rash includes PTs of erythema, exfoliative rash, ~~generalised erythema,~~ rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic;

Dermatitis includes PTs of dermatitis, and dermatitis allergic ~~and dermatitis exfoliative~~.

* As observed in post-marketing setting

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Geriatric Use

Of the ~~2351~~ 2901 patients with advanced solid tumors who received Lynparza ~~tablets 300 mg orally twice daily as monotherapy, 596 (25%)~~ as a single agent, 680 (23%) patients were aged ≥65 years, and this included ~~137~~ 206 (~~6~~7%) patients who were aged ≥75 years. ~~Seven~~ Thirteen (0.~~3~~4%) patients were aged ≥85 years.

5. PHARMACOLOGICAL PROPERTIES

First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

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All patients had a deleterious or suspected deleterious germline *BRCA*-mutation as detected by the Myriad BRAC*Analysis*® or BRACAnalysis CDx® at a central laboratory only (n=106), local *BRCA* test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in *BRCA1;* 69% had a mutation in *BRCA2*; and 1 patient (1%) had mutations in both *BRCA1* and *BRCA2*.

POLO demonstrated a statistically significant improvement in BICR-assessed PFS in patients randomized to Lynparza as compared with placebo. The final analysis of OS did not reach statistical significance.
Efficacy results of POLO are provided in Table 11 and Figure 9.

Table 11 Efficacy Results - POLO (BICR-assessed)

	Lynparza tablets (n=92)	**Placebo (n=62)**
Progression-Free Survival		
Number of events (%)*	60 (65%)	44 (71%)
Median, months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio** (95% CI)	0.53 (0.35, 0.81)	
p-value	0.0035	
Overall Survival		
Number of events (%)	61 (66)	47 (76)
Median, months (95% CI)	19.0 (15.3, 26.3)	19.2 (14.3, 26.1)
Hazard ratio† (95% CI)	0.83 (0.56, 1.22)	
p-value	0.3487	
Patients with Measurable Disease	n=78	n=52

Objective Response Rate (95% CI)	23% (14, 34)	12% (4, 23)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (21)	6 (12)
Duration of Response (DOR)		
Median time in months (95% CI)	25 (15, NC)	4 (2, NC)

* Number of events: Progression – Lynparza 55, placebo 44; death before BICR-documented progression – Lynparza 5, placebo 0
** Hazard ratio, 95% CI, and p-value calculated from a log-rank test. A hazard ratio <1 favors Lynparza.
NC Not calculable

~~The result of an OS interim analysis conducted based on 67% information fraction did not show a statistically significant improvement in OS for Lynparza compared to placebo.~~

מקרא לעדכונים המסומנים:
הוספת טקסט מהותי מסומנת בצבע אדום. 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
אסטרהזניקה (ישראל) בע"מ

אסטרהזניקה (ישראל) בע"מ, ת.ד 8044 , כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527