REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Lynparza
100 mg film-coated tablet x 56
150 mg film-coated tablet x 56
olaparib

Therapeutic indication(s)	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.
Start/end date of procedure	06.01.2020 – 04.06.2020
Final decision	To add a therapeutic indication in Annex 2 of the Positive Drug List (PDL) for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the value of the rendered medical services.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Lynparza

Health problem

Ovarian cancer comprises over 20 different types, which fall into three major groups: epithelial carcinoma (over 90%), germ cell carcinoma, and stromal cell tumors. Fallopian tube cancer and primary peritoneal cancer are morphologically similar to epithelial ovarian cancer, and the same approach is used in their treatment. Generally, the early stages of ovarian cancer are asymptomatic. As the disease progresses, abdominal pain, bloating, dyspepsia, irregular menstruation and fatigue appear. The most important risk factor for development of ovarian cancer is family history, often associated with a BRCA mutation. Deletions in the BRCA 1 and BRCA 2 genes are a strong risk factor for the development of breast and ovarian cancer. Mutations in BRCA 1 are twice as common as mutations in BRCA 2. Ovarian cancer is usually diagnosed at a late stage (in 75% of cases) and the quality of life of patients is one of the main factors that determine clinical decisions. For some patients, relieving the severity of symptoms, maintaining quality of life, and prolonging life are major therapeutic goals. Successful surgery results in long-term improvement in the quality of life of patients, associated with relief of symptoms and reduction of anxiety after surgery.

Olaparib is indicated and used as maintenance treatment in adult patients with platinum-sensitive recurrent high-grade epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who respond (complete or partial response) to platinum-based chemotherapy. The target population is adult patients with advanced (FIGO stage III and IV) high-grade epithelial ovarian cancer with BRCA1/2 mutation (germline and/or somatic), fallopian tube cancer, or primary peritoneal cancer who have responded (complete or partial response) after completion of first-line platinum-based chemotherapy.

Epidemiological data

In Bulgaria, ovarian cancer occupies the 12th place in newly diagnosed patients for 2018 - 712 cases. The registered deaths are 467. The five-year survival by stage is: 90% - I, 70% - II, 39% - III, 17% - IV, respectively. About 64% of the patients are diagnosed at advanced stage.

Efficacy data

The safety and efficacy of olaparib as maintenance therapy were investigated in a randomized, double-blind, placebo-controlled, multicenter, phase III clinical trial in patients with newly diagnosed advanced (FIGO stage III-IV) high-grade serous or endometrioid BRCA1/2, mutated BRCA1/2m ovarian cancer after completion of first-line platinum-based chemotherapy (SOLO-1). In this study, 391 patients were randomized 2:1 to receive Lynparza

(300 mg twice daily) or placebo. Patients were stratified according to the response to first-line platinum chemotherapy - complete response (CR) or partial response (PR). Treatment is continued until radiological progression of the underlying disease, occurrence of unacceptable toxicity or for a period of up to 2 years. In patients who retain a complete clinical response (i.e. without radiographic evidence of disease), the maximum duration of treatment is 2 years; however, patients with evidence of disease that remain stable (i.e. no evidence of disease progression) may continue to receive Lynparza for more than 2 years.

Progression-free survival (PFS)
The SOLO-1 study achieved its primary endpoint, demonstrating a significant improvement in progression-free survival (PFS) in olaparib-treated patients compared to placebo:

Statistically and clinically significant improvement in PFS, as assessed by the investigator:

- 70% reduction in the risk of progression or death at any time. The median PFS was not reached in the olaparib arm, in the placebo arm it was 13.8 months. The difference in median PFS between olaparib and placebo is expected to be within the range of about 3 years.
- The proportion of patients who remained progressive-free in the olaparib arm at 1, 2, 3, and 4 years was 87.7%, 73.6%, 60.4%, and 52.6%, respectively, versus 51.4%, 34.6%, 26.9% and 11.4% with placebo
- The superiority of olaparib in terms of PFS over placebo was demonstrated in all subgroups of patients
- There was a statistically and clinically significant reduction in the risk of progression or death in all olaparib arm patients (49-81%)

The clinical benefit beyond progression has been confirmed by:

- Statistically and clinically significant 50% reduction in the risk of second progression or death
- The delay of the time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST) is statistically and clinically significant
- The median of the OS is not reached in either arm.

Data reported by patients
The quality of life reported by patients in the SOLO-1 study was assessed with the FACT-O measure, while health status was assessed with the EQ-5D-5L questionnaire. The primary HRQoL analysis is the change from the baseline of the trial outcome index (TOI) at 24 months and the target FACT-O score. The TOI covers the following FACT-O subscales:

physical and functional well-being and additional concerns. There was no difference in the initial results of TOI and FACT-O in both arms of the study. The mean TOI score was 73.6 (olaparib) and 75.0 (placebo), respectively.

The effect of treatment and of disease stage on the utility of patients' health conditions was assessed through EQ-5D-5L. No deterioration or reduction of health-related quality of life is reported.

The EQ-5D-VAS (respondents' self-assessment) tool did not detect deterioration in patients' quality of life.

Safety data

Lynparza as monotherapy is associated with adverse reactions, usually mild or moderate, that generally do not require discontinuation of treatment. The most common adverse reactions in clinical trials in patients receiving Lynparza monotherapy were nausea, vomiting, diarrhea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anemia, neutropenia, thrombocytopenia and leukopenia. Adverse reactions grade ≥ 3 occurring in > 2% of patients are anemia, neutropenia, fatigue/asthenia, leukopenia, thrombocytopenia and vomiting. The most common side effects, leading to discontinuation and/or dose reduction are anemia, vomiting, nausea, fatigue/asthenia and neutropenia. The safety profile is based on pooled data from 1,826 patients with solid tumors treated with Lynparza as monotherapy.

Data on comparators

Bevacizumab monotherapy is the major comparator to olaparib for the treatment of patients with advanced (stage III and IV FIGO) high-grade epithelial ovarian cancer with a BRCA1/2 mutation (germline and/or somatic), fallopian tube cancer, or primary peritoneal cancer that have responded (complete or partial response) after completion of first-line platinum-based chemotherapy.
Bevacizumab is indicated as first-line treatment for ovarian cancer. Bevacizumab is administered as addition to carboplatin and paclitaxel for up to 6 cycles of treatment, followed by long-term use of bevacizumab as monotherapy until disease progression or a maximum of 15 months or occurrence of unacceptable toxicity.

Pharmacoeconomic indicators

Published health technology assessments of governmental institutions intended for the health care systems of other countries

Assessments of the reviewed health technology by the governmental institutions NICE (UK), TLV (Sweden), HAS (France), IQWiG (Germany) and SMC (Scotland) have been published, all recommending reimbursement.

Applied analysis

A cost-effectiveness analysis was performed to evaluate the value effectiveness of Lynparza with regard to the long-term measure life years gained (LYG) and a cost-benefit analysis to monitor changes in the quality of life of olaparib-treated patients compared to standard care via the QALY measure. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). The selected time horizon is lifelong - 50 years, and all significant costs and results are monitored, including the subpopulation of patients who are expected to have long-term survival after first-line platinum-based chemotherapy. As comparator, the best supportive care was chosen - routine monitoring (supportive care), which includes patients' follow-up and symptomatic treatment until progression.

Costs and results were modeled using a Markov model for a set time horizon of 50 years (lifelong) and the duration of the model was set using a Monte Carlo simulation based on Kaplan-Mayer survival curves. The Markov's model is built on the basis of three mutually exclusive health conditions – patients that didn't progress, sensitive to first-line therapy (PF), progressed patients (PD) and death. A discount with a 3.5% discount rate is applied.

The results of the analysis show that for both indicators - life years gained (LYG) and quality adjusted life years (QALY), Lynparza brings added benefits and is associated with a higher cost of QALY, with an incremental ratio exceeding 3 times GDP per capita. A deterministic sensitivity analysis was performed, which shows that the largest influence on the ICUR is exerted by the discount rate on the results, followed by overall survival data.
Subgroup analysis is not applied.

Costs of the assessed health technology

The model includes only direct medical costs - medication and patient follow-up (including costs of diagnostic procedures, examinations and tests).

Budget impact analysis

The budget impact analysis was conducted from the point of view of the paying institution - NHIF. The time horizon is 5 years. The size of the target population was estimated on the basis of epidemiological data from the National Cancer Registry. The estimated number of patients for the first year is 73 and for the fifth year - 192. Patients treated with olaparib as a first line will not be eligible for treatment with olaparib as a second line. The average duration of treatment for patients with olaparib is 24 months. If patients eligible for Lynparza were

treated with first-line bevacizumab, the duration of treatment is 14.7 months. If patients treated with first-line Lynparza are switched to second-line bevacizumab, the duration of treatment is 12.4 months.

A deterministic sensitivity analysis was performed in which the biggest impact on the budget impact would be the reduction or increase in olaparib costs by +/- 15%.

The budget impact of including olaparib as a first-line maintenance treatment in the Positive Drug List is negative and is associated with significant savings for the payer over the bevacizumab alternative, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The budget impact analysis shows that savings for the paying institution will be realized on reimbursement of olaparib as maintenance treatment in adult patients with advanced (FIGO stage III and IV) high-grade epithelial ovarian cancer with BRCA1/2 mutation (germline and/or somatic), fallopian tube cancer or primary peritoneal cancer that has responded (complete or partial response) following completion of first-line platinum-based chemotherapy.