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 treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer, having previously been treated with an anthracycline and a taxane unless patients were not suitable for these treatments.
Start/end date of procedure	11.06.2020 – 18.12.2020
Final decision	Inclusion of a new therapeutic indication in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act for payment by the National Health Insurance Fund (NHIF) beyond the cost of the rendered medical services with the following restriction: to be administered only in patients with triple-negative breast cancer.

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

Health problem

Breast cancer is the most common neoplasia in women worldwide and in Bulgaria and ranks second in cancer mortality after lung cancer. In general, metastatic breast cancer is still an incurable disease, with a total survival of about 3 years and a five-year survival 25%. World practice shows that the outcome of the disease and the prognosis for patients in the metastatic stage depends on the multidisciplinary oncological approach and on the access to new drug therapies.

The prognosis in patients with metastatic breast cancer is determined by many factors - hormonal status, HER 2 - receptor status, number of metastatic lesions, age of the patient, presence/absence of visceral crises, disease stage at the time of diagnosis and others.

The majority of patients have hormone-positive, HER2 negative breast cancer, most commonly aged about 55-60 years. Usually the disease progresses slowly and the possibility for several lines of endocrine therapy to be employed (in the absence of visceral crises) predetermines a better prognosis of the disease. On the other hand, germline mutation in the BRCA1 or BRCA2 gene leads to an increased risk of developing carcinoma of the breast and other organs, with a clinical syndrome of hereditary breast/ovarian cancer (HBOC), characterized by the occurrence of cancer in the family, including many relatives affected by breast and/or ovarian cancer diagnosed in early age. Large rearrangements and deletions in BRCA1 or BRCA2 can also functionally alter BRCA, leading to an identical clinical syndrome. Breast malignancies due to mutations in BRCA1 are more frequently of basal phenotype and are high-grade, while BRCA2-related tumors resemble sporadic tumors. Somatic mutations can also occur in BRCA genes of tumor cells.

The target population for olaparib treatment includes:
1. Patients with HER2-negative, locally advanced or metastatic breast cancer. Patients had to have been previously treated with anthracycline and taxane, administered as (neo)adjuvant therapy or for metastatic disease, unless they are not suitable for such treatment.
2. Patients with hormone receptor (HR) positive breast cancer had also to have progressed during or after previous endocrine therapy or be considered unsuitable for endocrine therapy.

Epidemiological data
Breast cancer is the most common neoplasia in women and the main cause of death in them after lung cancer. Epidemiological data for patients with gBRCAm and HER2-negative (whether a HR+ or a triple-negative breast cancer/TNBC) are lilmited worldwide, usually due to the need for highly specialized research. Morbidity is related to the age of the patients, with

older women having higher morbidity. Women aged 55-64 are most frequentlyly diagnosed, and the median age at the time of diagnosis is 62 years. At the time of diagnosis about 5-10% of women are in the metastatic stage. In terms of histological type, the majority of the tumors are HR+/HER2− (73%), about 12% are TNBC (HR−/HER2−). Data from the SEER registry show that patients with TNBC, HR+/HER2+ and HR−/HER2+ are 10-30% less likely to be diagnosed in older age compared to patients with HR+/HER2−. The likelihood of these patients being diagnosed in more advanced stage however is 6.4 to 20.0 times larger.

Efficacy data

The efficacy and safety of olaparib in patients with gBRCA1/2 mutations who have HER2-negative metastatic breast cancer have been studied in a randomized, open-label, controlled phase III clinical trial (OlympiAD). The control group included three chemotherapy options - capecitabine, vinorelbine or eribulin, with a ratio of olaparib to cytostatic patients therapy 2: 1. The primary endpoint of OlympiAD trial was to establish the efficacy of olaparib as monotherapy compared to alternative chemotherapy chosen by the treating physician (capecitabine, vinorelbine or eribulin) based on the period of progression-free survival (PFS). The secondary endpoints for the OlympiAD test are overall survival (OS), time to second progression (PFS2), degree of objective response (DOR), effect of olaparib on health-related quality of life, efficacy of olaparib in patients with an identified gBRCA mutation.

An advantage with respect to the primary endpoint for olaparib is observed in all subgroups with clinically significant reduction in the risk of disease progression or death in patients treated with olaparib (18% to 61%). The analysis in patients with gBRCA mutation also showed a significantly longer PFS in the olaparib group versus chemotherapy of a treating physician’s choice (7.4 versus 4.2 months). Response to treatment was observed in 59.9% in the olaparib arm and in 28.8% in the chemotherapy of the physician's choice group. A complete response was observed in 9.0% of patients with measurable disease in the olaparib group and 1.5% in the cohort treated with chemotherapy of physician's choice. In 52.0% of patients in the olaparib group a second progression or death were registered after the occurrence of an event related to the first progression (PFS2). The mean time to event of a second progression or death after the first progression was 13.2 months in the olaparib cohort and 9.3 months in the group of treating physician's chemotherapy choice. There was a statistically and clinically significant prolongation of the time to subsequent therapies or death in the olaparib arm relative to the treating physician’s choice therapy group, respectively 9.4 months compared with 4.2 months. Olaparib overall survival (OS) averaged 9.4 months compared to 4.2 months for chemotherapy selected by the physician. The clinical benefit of olaparib administration results in a delay of the need for initiation of the next line of antitumor therapy.

The mean time to death was 19.3 months in the olaparib group compared to 17.1 months in the cohort with therapy of physician's choice. The conducted additional subgroup analysis showed that the overall survival was the same in both arms regardless of whether patients have previously received systemic therapy for metastatic disease, regardless of hormonal status or whether part of the cytostatic treatment involved a platinum-based medicinal product.

Analysis of patient-reported data

The analysis shows that health-related quality of life (HRQoL) has improved to a greater extent in the olaparib group compared to the arm of treating physician-selected chemotherapy.

The proportion of patients who did not report deterioration in HRQoL in the sixth month of treatment was 81.5% in the olaparib arm versus 61.2% in treating physician-selected chemotherapy arm. At the twelfth month of treatment, these values were 64.0% vs 53.5% in the compared groups. Best overall clinically significant improvement in the indicator of overall health status/quality of life relative to baseline is registered in 38.8% of olaparib patients compared to 22.8% of those on treating physician-selected chemotherapy.

Safety data

Adverse reactions are usually mild or moderate in severity (Grade 1 or 2), usually not requiring discontinuation of treatment. The most commonly observed adverse reactions in clinical trials in patients receiving monotherapy with Lynparza (≥10%), are 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 adverse reactions that most often lead to discontinuation of treatment and/or dose reduction are anemia, vomiting, nausea, fatigue/asthenia and neutropenia. The adverse reactions that most frequently lead to permanent treatment cessation are anemia, nausea and thrombocytopenia.

There are no cases of myelodysplastic syndrome or acute myeloid leukemia pneumonitis, the incidence of a new primary tumor is low.

Data on comparators

Anthracyclines and taxanes are recommended as first-line therapy. In the majority of patients their effect is exhausted about a year after the commencement of treatment and the median overall survival is about 2-3 years. Once a given patient has been treated with anthracycline and taxane, the preferred chemotherapeutic agents are eribulin, capecitabine and vinorelbine.

Capecitabine is the most commonly used second-line product due to its efficacy, safety and the oral route of administration.

Increased toxicity and limited benefit in terms of overall survival has been observed with combination chemotherapy, its use in the treatment of metastatic breast cancer is limited and strictly individualized.

Pharmacoeconomic indicators

Published health technology assessments of government institutions intended for the purposes of other national healthcare systems

Assessments have been published by HAS, France and IQWiG, Germany, with both evaluations recommending reimbursement.

Applied analysis

The pharmacoeconomic cost-effectiveness and cost-benefit methods have been used, as gBRCA HER2- mBC affects both the expected duration and the quality of life of patients. In the cost-benefit analysis the measure of results is the quality adjusted life years (QALY), and in the cost effectiveness the life years gained (LYG). The perspective of the analysis is that of the paying institution - the National Health Insurance Fund. The time horizon is lifelong - 20 years. The main comparator in the analysis is chemotherapy, according to OlympiAD data and the recommendations of pharmacotherapeutic guidelines. All costs and results in the analysis are discounted by 3.5% on an annual basis. A segmented survival model was employed with 3 states: progression free (PF), progressed (PD) and death. The results of the analysis show that the additional costs for an additional year of life gained and an additional QALY exceed three times the gross domestic product per capita.

Costs of the assessed health technology

The model includes the costs of drug therapy with alternatives, costs for the administration of comparative alternatives as well as treatment costs after progression with the assessed technology and after progression with therapeutic alternatives. The cost of subsequent treatment includes the cost of drug therapy and its administration.
Cost of determining the BRCA mutation is not included.

Budget impact analysis

The analysis of the budget impact is prepared from the perspective of the payer - The National Health Insurance Fund, the time horizon is 5 years. The target population is the sum of TNBC patients treated with anthracycline or taxane, and HER2-/ HR+ patients after previous treatment with an anthracycline or taxane. The total number of patients is 63 in the first year, rising to 67 in the fifth year. The assessed health technology leads to additional costs for the paying institution in the 5-year period of analysis, without taking into account risk-sharing

agreements and patient access schemes. The additional costs are accompanied by additional benefits for the patients.

Conclusion

Lynparza (olaparib) is the first PARP inhibitor approved for the treatment of patients with germline BRCA mutations and HER2-negative metastatic breast cancer. The clinical benefit of olaparib includes prolonged PFS and improved frequency of objective response, which are associated with improved health - related quality of life (HRQoL), assessed by several indicators, as compared to treating physician-selected chemotherapy. Olaparib also reduces the risk of disease progression or death. These additional benefits come with additional cost for the paying institution.