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

HEALTH TECHNOLOGY ASSESSMENT

Ibrance
125 mg capsule, hard x 21
palbociclib

Therapeutic indication(s)	Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer: - in combination with an aromatase inhibitor. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
Start/end date of procedure	27.02.2019 – 20.09.2020
Final decision	To add a 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 and payment by the National Health Insurance Fund (NHIF) beyond the cost of rendered medical services.

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

Health problem

Disease epidemiology data are based on the National Cancer Registry local data. According to the presented data, breast cancer in Bulgaria is the most frequent of all malignant diseases in women with a rate of 26.4%, the incidence and mortality being higher than the European average.

The disease five-year relative survival for Bulgaria is 72.8%, which is lower than the EU average of 83.8%.

The target population is patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

Patients follow-up should be carried out in line with the adopted requirements of the NHIF for the follow-up of patients with oncological diseases, based on the current local recommendations, adopted by the Bulgarian Cancer Scientific Society, and the assessment by the attending physician (with consideration of patient's condition and should a more frequent monitoring of therapy is required).

Efficacy data

Palbociclib (Ibrance) is a new, the first in its class, highly selective reversible inhibitor, used in combination with an aromatase inhibitor, and in women who have received previous endocrine therapy - in combination with fulvestrant. It acts synergistically with letrozole/fulvestrant, leading to significantly higher progression-free survival compared to letrozole/fulvestrant monotherapy, with a manageable toxicity profile and without significant deterioration in health-related quality of life in untreated postmenopausal women with advanced or metastatic ER + /HER2- breast cancer.

Ibrance is intended for oral use. The recommended dosage in the summary of product characteristics is a single daily dose of 125 mg for 21 consecutive days, followed by 7 days without treatment, ending the therapeutic cycle of 28 days. Palbociclib treatment should be continued for as long as the patient has clinical benefit or until unacceptable toxicity occurs.

Ibrance belongs to antineoplastic agents protein kinase inhibitors, and has the ATC code: L01XE33.

The completed and ongoing studies used in the comparative analysis of the therapeutic efficacy/effectiveness and safety of Palbociclib are:

- PALOMA-1: A randomized, parallel comparison, phase II clinical trial examining the efficacy and safety of PAL plus letrozole versus letrozole in untreated postmenopausal women with HR + /HER2 breast cancer.
- PALOMA-2: An ongoing, multicenter, double-blind, phase III study comparing the efficacy and safety of PAL plus letrozole versus letrozole plus placebo in untreated postmenopausal women with HR + / HER2− advanced / metastatic breast cancer.
- PALOMA-3: A multicenter, randomized, double-blind, phase III study comparing PAL plus fulvestrant versus fulvestrant plus placebo in women with HR + /HER2− advanced/metastatic breast cancer undergoing endocrine therapy.

The analyzed and summarized results from the phase II-III clinical trials (PALOMA-1, PALOMA-2, PALOMA-3) show that:

Palbociclib in combination with letrozole leads to statistically and clinically significant improvement in progression-free survival compared with letrozole monotherapy (PFS 27.6 months vs. 14.5 months) in untreated postmenopausal women with HR + / HER2− advanced / metastatic breast cancer. The benefit of the combined intervention for PFS is also maintained in the individual demographic subgroups of patients. Palbociclib + letrozole combination therapy significantly improved the response rate to clinical benefits compared to letrozole monotherapy.

With palbociclib + letrozole combination therapy, no significant deterioration was observed compared to baseline in the physical, social, functional and emotional state of the participants compared to letrozole monotherapy. Retention of health status with the combination regimen did not differ significantly from that of letrozole monotherapy.

Results of PALOMA-3 clinical trial show that palbociclib in combination with fulvestrant significantly prolonged progression-free survival compared to fulvestrant monotherapy (11.2 months versus 4.6 months) in women with HR + / HER2− advanced/metastatic breast cancer that have progressed against the background of previous endocrine therapy. The superiority of palbociclib + fulvestrant over fulvestrant monotherapy in terms of PFS was retained irrespective of the degree of endocrine resistance, hormone receptor expression levels, and tumor PIK3CA mutation status. Clinical benefits were observed in 2/3 of patients receiving the combination. Treatment of patients with palbociclib + fulvestrant was associated with a higher rate of objective response (confirmed partial or complete) to treatment compared to fulvestrant monotherapy (OR 2.69, 95% CI 1.43-5.26; p = 0.0012).

Palbociclib + fulvestrant therapy preserved patients' quality of life compared to fulvestrant monotherapy, in which a deterioration compared to baseline was seen. The inclusion of palbociclib significantly reduces the deterioration of quality of life.

Objective analysis of the health outcomes in each study:

PALOMA-1: The primary endpoint of the study was PFS, defined as the time from randomization to objective disease progression or death. Palbociclib + letrozole therapy resulted in a statistically significant improvement in PFS values compared to letrozole monotherapy (20.2 vs 10.2 months).

PALOMA-2: The primary endpoint of the study was PFS, defined as the time from randomization to the time of radiographic confirmation of disease progression in line with RECIST (version 1.1), or death during the study. PFS of 27.6 months for the palbociclib + letrozole group demonstrated superiority over PFS of 14.5 months reported in the placebo + letrozole group, where PFS values were established by the investigator.

PALOMA-3: The primary endpoint of the study was PFS as determined by the investigator according to RECIST (version 1.1). PFS is defined as the time from randomization to the time of radiological confirmation of disease progression or death during the study. The mean PFS value for the palbociclib + fulvestrant group was statistically significantly better compared with fulvestrant + placebo control group, 11.2 months vs 4.6 months in the ITT analysis by the investigator.

A meta-analysis of Palbociclib vs. Endocrine Therapies:

The main purpose of the meta-analysis was to assess the efficacy and safety of the new health technology palbociclib in combination with letrozole or fulvestrant, compared to other endocrine therapies used as first and second line treatments for ER-positive, HER2-negative locally advanced or metastatic breast cancer.

Main analysis: Compared to the fixed-effects model, palbociclib + letrozole is statistically significantly a better therapy than the three comparators - letrozole, tamoxifen and anastrozole with a PFS risk factor (HR) of 0.41 to 0.58. The palbociclib + letrozole combination is most likely to be ranked as the best therapy among the 4 comparators (99.8%), with the SUCRA (surface under the cumulative ranking) value (99.9%) being almost 100%.

Regarding PFS, palbociclib + fulvestrant 500 mg is statistically significantly a better therapy than comparators fulvestrant 250 mg, fulvestrant 500 mg, fulvestrant 500/250 mg, anastrozole 1 mg, letrozole 2.5 mg, exemestane 25 mg, megestrol acetate 160 mg and aminoglutethiminde

500 mg + corticosteroid, with PFS HR 0.26 to 0.46. No statistically significant difference was achieved with everolimus 10 mg + exemestane 25 mg (HR at PFS 1.03; 95% CrI, 0.58-1.76). The palbociclib + fulvestrant 500 mg combination is most likely to be ranked as second best therapy among the 10 therapies compared (45%). Everolimus 10 mg + exemestane 25 mg and palbociclib + fulvestrant 500 mg have the two highest and similar SUCRA values - 95% and 93.9%, respectively.

A meta-analysis of Palbociclib vs. Chemo:

Results: The studies were subdivided based on line of therapy and results: 22 studies were included in the first line PFS/TTP meta-analysis, 23 studies were included in the first line OS meta-analysis, 44 studies were included in the second line PFS/TTP meta-analysis and 37 studies were included in the second line OS meta-analysis.

First line PFS: Includes a total of 8152 patients. Statistically significant differences in PFS/ TTP were found in favor of the combination palbociclib + letrozole compared to anastrozole, letrozole, exemestane, tamoxifen, fluorouracil + epirubicin + cyclophosphamide, megestrol acetate, capecitabine (uneven) + metcloxoate + 5-cyclorexate + in the fixed-effects model. The palbociclib + letrozole combination is also most likely to be ranked as the best therapy with the highest SUCRA (Surface Under the Cumulative Ranking curve) value.

First line OS: A total of 7889 patients have been included. Palbociclib + letrozole resulted in a statistically insignificant improvement in OS compared to all other therapies with exception of liposomal doxorubicin, docetaxel + bevacizumab, docetaxel and paclitaxel + bevacizumab in the fixed-effects model. Palbociclib + letrozole combination has the highest SUCRA value (76%) among all therapies except liposomal doxorubicin, docetaxel + bevacizumab and docetaxel paclitaxel + bevacizumab, ranking second (19.3%) in the likelihood of being the best choice of therapy.

Second line PFS: Includes a total of 14,708 patients. A statistically significant difference in PFS/TTP was found in favor of palbociclib + fulvestrant compared to letrozole, exemestane, anastrozole, fulvestrant, fluorouracil + epirubicin + cyclophosphamide, megestrol acetate, capecitabine (uneven), aminoglutecitarone + corticosteroid, mitoxantrone, cpecitabine (continuous) capecitabine + sunitinib, cyclophosphamide + methotrexate + 5-fluorouracil, paclitaxel + capecitabine, paclitaxel + epirubicin + capecitabine and pegylated liposomal doxorubicin in the fixed-effects model. The combination of palbociclib + fulvestrant also has the highest SUCRA value (97.2%) among all therapies, with a third largest value (18.9%) for the likelihood of being the best therapy.

Second line OS: Includes a total of 12,908 patients. Palbociclib + fulvestrant is not associated with a statistically significant improvement in OS compared to various chemotherapeutic drugs. The combination of palbociclib + fulvestrant was associated with an improvement in OS compared to all therapies except docetaxel 100 mg, doxorubicin + vinorelbine, paclitaxel + bevacizumab, doxorubicin, docetaxel + sunitinib, everolimus + exemestane, paclitaxel, exemestane, nab-paclitaxel + bevacizumab, fulvestrant 500 mg and paclitaxel + bevacizumab + gemcitabine in the fixed-effects model. The palbociclib + fulvestrant combination is characterized by a SUCRA value of 55.95% and a 17.53% probability for being selected as the best therapy.

Summary of PFS/TTP first line sensitivity analyses:
For each sensitivity analysis, palbociclib + letrozole combination was associated with an improvement in PFS/TTP over all other therapies.

Summary of first-line OS sensitivity analyses:
For each sensitivity analysis, the palbociclib + letrozole combination was associated with improvement in OS compared to all other therapies except pegylated liposomal doxorubicin, docetaxel + bevacizumab 15 mg, docetaxel 100 mg, paclitaxel + bevacizumab and docetaxel + bevacizumab 7.5 mg.

Summary of PFS/TTP second line sensitivity analyzes:
For each sensitivity analysis, the combination palbociclib + letrozole is associated with an improvement in PFS/TTP compared to all other therapies except everolimus + exemestane.

Summary of second-line OS sensitivity analyses:
For each each sensitivity analysis, the combination of palbociclib + letrozole was associated with an improvement in OS compared to all other therapies except docetaxel 100 mg, doxorubicin + vinorelbine, paclitaxel + bevacizumab, doxorubicin, docetaxel + sunitinib, exstanelime + fulvestrant 500 mg.

Safety data

Outcome analysis of the conducted phase III clinical trials (PALOMA-2, PALOMA-3) shows that:
Adverse reactions reported with palbociclib plus letrozole in untreated women with ER + / HER2− advanced/metastatic breast cancer have been identified as tolerable and manageable.

The inclusion of palbociclib to letrozole preserves the health-related quality of life of untreated postmenopausal women with ER + / HER2− advanced/metastatic breast cancer, with no significant difference in quality of life compared to letrozole therapy. The

development of neutropenia had no significant effect on fatigue and overall quality of life in patients treated with palbociclib plus letrozole.

With palbociclib and letrozole combination therapy, there was no significant deterioration from baseline in the physical, social, functional and emotional state of the patients compared to letrozole monotherapy. Preserving the health status with the combination regimen did not differ significantly from that with letrozole monotherapy.

Adverse reactions reported with palbociclib plus fulvestrant have been identified as tolerable and can be controlled by reduction or discontinuation of the intake or by standard medical therapy. The rate of grade 5 adverse reactions remains low. The rate of therapy discontinuation due to adverse reactions is also low. The development of neutropenia as a result of palbociclib use is a reversible process controlled by changing the dose without losing the efficacy of the therapy. The development of neutropenia had no significant effect on fatigue and overall quality of life in patients treated with palbociclib plus fulvestrant.

Patients' quality of life was retained with palbociclib plus fulvestrant therapy compared to fulvestrant monotherapy, in which a deterioration compared to baseline was seen. The inclusion of palbociclib significantly reduces the deterioration of quality of life. The combination therapy also significantly improved the emotional status of patients compared to fulvestrant monotherapy.

The most common (≥ 20%) adverse reactions of any degree reported in patients receiving palbocyclib in randomized clinical trials were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia and diarrhea. The most common (≥ 2%) adverse reactions grade ≥ 3 to palbociclib were neutropenia, leukopenia, anemia, fatigue and infections.

Reduction or changes in the dosage due to adverse reactions were observed in 34.4% of patients receiving palbociclib in randomized clinical trials, regardless of the combination.

Definitive discontinuation, due to adverse reactions occurred in 4.1% of patients receiving palbociclib in randomized clinical trials, regardless of the combination.

Data on comparators

The main compared technologies, included in the Pharmacotherapeutic guide on medical oncology and available in PDL in Bulgaria, are:

- Anastrozole
- Letrozole
- Fulvestrant

- Exemestane
- Everolimus (+exemestane)

Pharmacoeconomic indicators

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

Assessments of palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor have been conducted by NICE (England), TLV (Sweden) and HAS (France), all being positive, with NICE having imposed a condition for a discount under the patient access scheme.

Applied analysis

Value efficiency of a change in the therapeutic indications of the medicinal product Ibrance 125 mg x 21 to add an indication for first-line therapy was assessed. The selected method for comparative assessment of the medicinal product Ibrance and therapeutic alternatives is a cost-benefit economic analysis. The analysis was performed from the perspective of the paying institution, the NHIF, with a lifelong time horizon.

The cost-benefit modeling is based on a semi-Markov model, which uses the results of therapeutic efficacy data, measured and identified in PALOMA 1 and PALOMA 2 clinical trials, as well as a meta-analysis applied for indirect comparison with therapeutic alternatives, the data being used are based on six economic studies. The employed outcome measure was quality-adjusted life year (QALY), as well as progression-free survival (PFS) compared to the therapeutic alternative with the same mechanism of action - a selective inhibitor of cyclin-dependent kinases - Ribociclib.

The course of the disease has been described through three independent health conditions - no progression, progression and death.

Ibrance in combination with Letrozole, used as a first line therapy, dominates in relation to ICER over Ribociclib + Letrozole and is a cost-effective medicinal product, compared to Everolimus + Exemestane, with ICER being less than three times lower than GDP per capita. Ibrance in combination with Letrozole, administered as a first line compared to Letrozole, Exemestan and Fulvestrant, has an additional cost for an additional quality-adjusted life year, which exceeds 3 times the GDP per capita. Indirect comparison of Palbociclib and Ribociclib in a meta-analysis shows a difference in progression-free survival with Palbociclib + Letrozole versus Riboclib + Letrozole, with Palbociclib + Letrozole therapy having an advantage (higher PFS and lower costs).

A sensitivity analysis was conducted, with results confirming the main scenario.

Costs for the assessed health technology

Annual costs of drug therapy have been calculated according to the dosage in the SPC, without taking into account other direct or indirect costs, related to the therapy.

Budget impact analysis

The analysis of the budget impact has been conducted from the paying institution, the NHIF, perspective with a time horizon of 5 years.

In the analysis, only the expected number of patients treated with first-line therapy have been considered - 29 for the first year, increasing to 368 through the fifth year since entering the market. Expenses have not been discounted. Two scenarios have been considered - a main one in which the NHIF allows both Palbociclib and Ribociclib to be paid, and an additional in which it is assumed that Palbociclib will be paid while Ribociclib will not be paid. In both scenarios, the payment of Palbociclib as a first-line therapy is associated with an increase in the costs for the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Based on the assessment of the evidence for efficacy, safety, real world experience and pharmacoeconomic data for the use of Palbociclib (Ibrance) in combination with letrozole for the treatment of first-line patients in HR +/ HER2/negative/metastatic breast cancer, the evidence supports the inclusion of the therapeutic indication in the Positive Drug List of the Republic of Bulgaria. The medicinal product has been shown to be effective, safe and to have a positive impact on the health-related quality of life. The pharmacoeconomic analysis found that the inclusion of the therapeutic indication is associated with an increased cost to the payer, but at the same time leads to improved health outcomes.