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

HEALTH TECHNOLOGY ASSESSMENT

Verzenios
50 mg film coated tablet x 42
100 mg film coated tablet x 42
150 mg film coated tablet x 42
abemaciclib

Therapeutic indication(s)	Indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
Start/end date of procedure	19.04.2019 – 25.11.2019
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 with an obligation to monitor the effect of therapy in line with adopted conditions and criteria. Rejects inclusion in Annex 1 of the PDL for home treatment of diseases, paid for by the NHIF.

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

Health problem

Breast cancer is a progressive disease that develops due to abnormal cell growth in the breast tissue. A series of genetic and epigenetic changes lead to uncontrolled cell proliferation and tumor formations. These changes/aberrations can be hereditary and/or manifest throughout one's life. According to the International Classification of Diseases (ICD), breast cancer has ICD code C50.

Breast cancer has multiple risk factors. The most common symptoms of breast cancer are the appearance of a formation and a change in the shape and appearance of the breast.

Breast cancer is highly heterogeneous, but it can be classified according to its staging and molecular profiling. The progression of breast cancer has the following sequence: non-invasive - invasive - metastatic disease. It was ascertained that 30% of women diagnosed with early-stage breast cancer progress to locally advanced or metastatic cancer. While the initial disease can be cured, locally advanced or metastatic breast cancer remains incurable. In metastatic disease, survival varies from several months to many years (median survival 2 years). Four major molecular subtypes of breast cancer have been identified based on the expression of receptors (HR and HER2) and Ki67 (a marker of cell proliferation). The most commonly diagnosed molecular subtype is Luminal A (HR+/HER2-).

Advanced (locally advanced and metastatic) HR+/HER2- breast cancer is associated with a significant burden on the patient's health related quality of life (HRQoL), deterioration of social life and reduced ability to perform daily activities. HRQoL at an advanced stage of the disease is adversely affected by many factors such as deterioration of physical and emotional state, and the severity of symptoms.

HR+/HER2- locally advanced or metastatic breast cancer still remains an incurable disease. The main goal of various therapies is to delay the progression of the disease, prolong overall survival and improve the quality of life of patients. The need for new therapies to help achieve the goals of treatment remains significant.

Verzenios (abemaciclib) is indicated for the treatment of women with HR+/HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have previously received endocrine therapy.

Abemaciclib (VerzeniosTM) is a targeted treatment, an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), which allows the "rebound" phenomenon in the cell cycle to be avoided and leads to inhibition of tumor growth.

It is the first and only inhibitor that can be taken daily, twice a day. Because abemaciclib is a medicine intended for oral use and not an infusion, this allows for more flexibility in the patients' everyday life. With its therapeutic efficacy similar to other CDK4 and 6 inhibitors, a predictable, manageable safety profile and a convenient dosage regimen, abemaciclib represents a valuable addition to the treatment options currently used.

Epidemiological data

Breast cancer is the most common type of cancer in women across Europe. Data on the incidence of HR+/HER2- breast cancer in Europe are relatively limited. Data from two observational, multinational studies indicate that 50-60% of women with metastatic breast cancer in Europe are of the HR+/HER2 subtype.

According to the Bulgarian National Cancer Registry from 2017, breast cancer holds the first place in frequency in women, representing 26.8% of all malignancies in them.

The majority of breast cancers develop in the epithelial cells of the ducts (ductal carcinoma) or lobules (lobular carcinoma). As the cancer progresses, it spreads to adjacent adipose and fibrous tissues, lymph nodes, and can metastasize to other parts of the body.

Breast cancer is highly heterogeneous, but it can be classified on the basis of staging and molecular profiling. The classification is indicative of how quickly the cancer develops and spreads.

There are three classes of therapy for HR+/HER2- locally advanced or metastatic breast cancer - endocrine therapy (or hormone therapy), targeted therapy and chemotherapy. Each class is administered as monotherapy or in combination with another class of therapy.

Efficacy data

To evaluate the therapeutic efficacy and safety of the new abemaciclib health technology, the results of four clinical trials have been analyzed and summarized, as well as data from a comparison of abemaciclib with palbociclib and ribociclib.

• JPBA clinical study, evaluating the safety of abemaciclib in patients with advanced cancer (breast cancer, non-small cell lung cancer, glioblastoma, melanoma and colorectal cancer).

• MONARCH 1 clinical trial, evaluating the antitumor activity and safety profile of 200 mg abemaciclib monotherapy in patients with HR+/HER2-metastatic breast cancer, progressing after endocrine therapy and 1–2 chemotherapy regimens.
• MONARCH 2 clinical trial, evaluating the efficacy of 150 mg abemaciclib in combination with fulvestrant versus fulvestrant in patients with HR+/HER2-advanced breast cancer.
• MONARCH 3 clinical trial, evaluating the efficacy of abemaciclib in combination with NSAI (letrozole or anastrozole) in postmenopausal women with advanced breast cancer. The results show superiority of abemaciclib therapies over comparators.
• Comparison of CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer with disease progression after endocrine therapy in combination with a target agent.

An indirect comparison of abemaciclib with palbociclib shows that in patients with HR+/HER2- locally advanced or metastatic breast cancer with prior endocrine therapy, PFS was 16.4 months for abemaciclib/fulvestrant (MONARCH 2) versus 11.2 for palbociclib/ fulvestrant 3). PFS in the placebo/fulvestrant groups in the respective studies was 9.3 and 4.6. When comparing the data, the differences in the studied populations should be taken into account - for example in PALOMA-3, 32.6% of the patients received chemotherapy for the treatment of metastases, while in MONARCH 2 the population was homogeneous and patients did not receive chemotherapy.

The evaluation of the comparative therapeutic efficacy of abemaciclib versus palbociclib (in combination with letrozole/fulvestrant) in patients who have recently received endocrine therapy under (neo)adjuvant conditions and in patients with previous endocrine therapy for advanced disease, did not find a statistically significant advantage of either of the two combinations.

Analysis of data reported by patients
Treatment with abemaciclib/fulvestrant was associated with a small, insignificant reduction in baseline pain compared to placebo/fulvestrant (measured by the mBPI questionnaire). The changes in HRQoL parameters were similar between the abemaciclib/fulvestrant and placebo/fulvestrant arms. Analysis of data from the EORTC QLQ-C30 shows that changes in scores for physical, role, cognitive, emotional, and social functioning are similar between the arms.

MONARCH 2 and PALOMA-3 - quality of life: in MONARCH 2 the changes in HRQoL scores are similar between abemaciclib/fulvestrant and placebo/fulvestrant; in PALOMA-3, changes in HRQoL scores were statistically significant in treatment arms for global HRQoL, emotional functioning and pain, in favor of palbociclib/fulvestrant versus placebo/fulvestrant.

Safety data

The safety profile of abemaciclib in clinical trials indicates a higher incidence of ADR observed in the palbococlib groups compared to comparators. The most common ADR are diarrhea, fatigue, nausea, abdominal pain and neutropenia.

Safety profile of the comparison of abemaciclib and palbociclib, assessed in MONARCH 2 and PALOMA-3: abemaciclib-fulvestrant (ABE-FUL) and palbociclib-fulvestrant (PAL-FUL) have a comparable safety profile.
A comparison of CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer with disease progression after endocrine therapy in combination with a target agent found that the rate of "any adverse event" is similar, which also applies to non-haematological ADR, haematological ADR and non-haematological abnormal laboratory results. Differences > 15% were observed only for diarrhea, leukopenia and thrombocytopenia, with larger differences with abemaciclib.

Data on comparators

Ibrance (palbociclib), included in PDL, has been selected as a comparative alternative, which is a targeted treatment, inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), indicated for the treatment of HR+/HER2-locally advanced or metastatic breast cancer.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions, intended for the health care systems of other countries
Five assessments of Verzenios health technology have been carried and published by government institutions for the purposes of the corresponding national healthcare systems: NICE, UK (2018, 2019), HAS, France (2018), IQWIG, Germany (2018) and TLV (Sweden, 2019).

NICE from the United Kingdom and the Swedish TLV agency recommend reimbursing the abemaciclib health technology, while the French agency HAS is conducting an additional assessment. According to the IQWIG assessment, there is little benefit in some patient populations, and no additional benefit of abemaciclib has been demonstrated in others.

Applied analysis
A minimum cost analysis has been employed. No measure of outcomes or modeling has been presented, given the equivalent therapeutic outcomes of the pharmacoeconomic analysis. A comparative alternative is palbociclib (CDK4,6 inhibitor), the perspective of the analysis is

that of the National Health Insurance Fund (NHIF), the time horizon is consistent with the development of the disease, the discounting level of costs and results - 3.5%.

The results of an indirect comparison of MONARCH 3, PALOMA 2 and PALOMA 1/ TRIO-18 studies (phase II) have been presented. PFS, OS, ORR, CBR were used as outcome measures. Based on the results, it can be concluded that the CDK 4/6 inhibitors abemaciclib and palbociclib (in the context of initial endocrine-based therapy in locally advanced or metastatic disease) did not show statistically significant differences ($p < 0.05$) in terms of therapeutic efficacy and safety profile.

CDK4/6 inhibitor therapy in combination with an aromatase inhibitor (AI) significantly increased the median duration of PFS compared with placebo.

Two scenarios for therapy in the context of initial treatment have been considered:

- in combination with letrozole
- in combination with fulvestrant

The results of the analysis show that abemaciclib in combination with letrozole leads to savings for the health system compared to the alternative palbociclib + letrozole in terms of initial therapy for advanced or metastatic breast cancer. In a mixed patient population, including patients on both initial therapy for metastatic disease and patients after failure of previous therapy for this condition, abemaciclib + fulvestrant has a higher treatment cost than palbociclib + fulvestrant.

Analyses of subgroups

Due to the fact that abemaciclib is used in a specific group of patients with HR+, HER2- locally advanced or metastatic breast cancer, no subgroup analysis has been presented.

Costs for the assessed health technology

Only acquisition costs of medications were calculated, costs of specialized medical services, as well as those for follow-up were not included, given their similar value for all compared drugs for the treatment of HR+/HER2-locally advanced or metastatic breast cancer.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying public institution, the NHIF. The time horizon is 5 years. The estimated number of patients eligible for treatment with Verzenios and alternatives (patients who have not received systemic therapy for advanced or metastatic disease and patients with endocrine resistance) for the next

5 years was indicated, expected to increase each year: for year 1 the number of patients is projected to be 167, reaching 927 in year 5.

Sensitivity analysis has been performed, the attached tornado diagrams show that the budget impact is largely determined by the price of palbociclib and abemaciclib.

Following the inclusion of Verzenios in the PDL as first-line therapy, a realization of savings is expected for each year over the time horizon. When treatment with Verzenios is paid as second-line therapy to patients after primary and/or secondary endocrine resistance (second-line therapy) HR+/HER2- locally advanced or metastatic breast cancer, additional costs are expected to be generated over the time horizon, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The medicinal product is an additional alternative for women with hormone receptor (HR) positive, human epidermal growth factor receptor (HER2) negative, locally advanced or metastatic breast cancer: in combination with an aromatase inhibitor or fulvestrant as a baseline endocrine therapy, or in women who have previously received endocrine therapy. The use of the medicinal product Verzenios as a first line treatment is expected to generate savings for the health insurance fund, while as a second line - additional costs.

An advantage of the proposed technology is an uninterrupted oral drug administration. This allows for greater flexibility in patients' everyday life in the treatment of a chronic disease.