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

HEALTH TECHNOLOGY ASSESSMENT

Kadcyla

160 mg/8 ml powder for concentrate for solution for infusion x 1 vial

100 mg/5 ml powder for concentrate for solution for infusion x 1 vial

Trastuzumab emtansine

Therapeutic indication(s)	As a single agent indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy.
Start/end date of procedure	28.05.2020 – 11.12.2020
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.

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

Health problem

Breast cancer (BC) is the most commonly diagnosed cancer. BC is the most common oncological cause of death in women. Early breast cancer (EBC) is an oncological condition with no spread beyond the breast or axillary lymph nodes. Malignancies with HER2 overexpression are caused by abnormal HER2 signaling, which leads to increased tumor aggressiveness, higher risk of relapse, less time to a relapse, and higher mortality compared to HER2-negative malignancies.

In HER2+ breast cancer, a positive hormone receptor status usually serves as a predictor of an indolent, slow-growing tumor with a longer time to a relapse. In patients with HER2+ EBC population with negative HR status the risk of recurrence is high and it occurs earlier. HER2 overexpression has been associated with tumor aggressiveness and proliferation, as well as decreased overall survival (OS).

Patients with breast cancer (including patients with EBC) have a decreased health related quality of life (HRQoL). Women with breast cancer have a higher risk of fatigue, sexual dysfunction and infertility, as well as stress and mental illness.

Kadcyla (trastuzumab emtansine) is recommended in international guidelines for the treatment of HER2-positive cancer at an early stage, in residual invasive disease after neoadjuvant therapy (NCCN and ESMO). Kadcyla (trastuzumab emtansine) is also recommended by ESMO after first-line trastuzumab-based therapy. In the Bulgarian Pharmacotherapeutic Guide, trastuzumab emtansine is recommended as adjuvant therapy for the treatment of HER2-positive cancer at an early stage, with residual invasive disease in the breast or axilla, after neoadjuvant systemic therapy, including anti-HER2 therapy.

Epidemiological data

In Bulgaria, 4,016 cases of breast cancer were newly diagnosed in 2018, all of them in female patients (25.7% of all cancer cases). Each year in Bulgaria there are approximately 1,387 deaths caused by breast cancer, about 7% of patients die.

Nearly 15% - 20% of all BC cases are related to HER2 overproduction. The cases of HER2-positive BC in Bulgaria are about 600 to 800.

Efficacy data

The therapeutic efficacy and safety profile of trastuzumab emtansine versus trastuzumab as adjuvant therapy in patients with HER2-positive breast cancer who have a residual tumor in the breast or axillary lymph nodes after preoperative therapy were analyzed in the KATHERINE clinical trial.

Endpoints

The primary endpoint of the study was invasive disease-free survival (iDFS), and the secondary endpoints included OS and patient-reported outcomes (PRO).

Efficacy of trastuzumab emtansine in early breast cancer

KATHERINE achieved its primary endpoint, with a statistically and clinically significant improvement in iDFS for trastuzumab emtansine compared to trastuzumab in patients with HER2+ EBC, with residual invasive disease after completion of neoadjuvant treatment. A 50% reduction in the risk of recurrence or death was observed in patients receiving trastuzumab emtansine. The 3-year incidence of event-free iDFS (EFR) increased from 77.0% for trastuzumab to 88.3% for trastuzumab emtansine (difference 11.3%). Secondary endpoint results support the clinical benefit of trastuzumab emtansine compared to trastuzumab in patients with early breast cancer.

Secondary efficacy endpoints: iDFS, including second primary non-breast cancer (iDFS-SPNBC).

Trastuzumab emtansine treatment improved iDFS-SPNBC compared to trastuzumab. The benefit of trastuzumab emtansine in patients with EBC occurred rapidly after initiation of treatment and was maintained during further follow-up compared to trastuzumab.

Disease-free survival

Trastuzumab emtansine treatment resulted in improved disease-free survival (DFS) compared to trastuzumab. DFS's three-year EFR was 87.41% versus 76.89% in the trastuzumab emtansine and trastuzumab arms, respectively.

Overall survival

The estimated 3-year OS is 95.2% for trastuzumab emtansine versus 93.6% for trastuzumab. The estimated 5-year OS is 92.1% for trastuzumab emtansine compared to 86.8% for trastuzumab.

Distance recurrence-free interval (DRFI)

Trastuzumab emtansine treatment improved DRFI compared to trastuzumab. The DRFI EFR projections for year 3 were 89.7% versus 83.01% in the trastuzumab emtansine and trastuzumab arms, respectively.

Patient-reported outcomes

No clinically significant deterioration from baseline was observed in the mean population scores for the General Health Status Scale/HRQoL, all five functional scales (physical, role, cognitive, emotional, social) measured by EORTC QLQ-C30, and all four functioning scales (body perception, future perspective, sexual function and sexual pleasure), measured by EORTC QLQ-BR23. Mean general health status and baseline functioning were maintained during adjuvant treatment.

Safety data

Trastuzumab emtansine has been evaluated for the treatment of HER2-positive, locally advanced inoperable or MBC, HER2-positive early-stage HER2 breast cancer and non-small cell lung cancer (NSCLC).

The safety data obtained during the reporting interval are consistent with the known safety profile of trastuzumab emtansine. Overall, the benefit-risk profile of trastuzumab emanzine in the approved indications remains favorable.

The safety of trastuzumab emtansin was evaluated in clinical trials in 2,611 patients with early breast cancer. In this patient population:

- The most common serious adverse reactions (ADR) are haemorrhage, pyrexia, thrombocytopenia, dyspnoea, abdominal pain, musculoskeletal pain and vomiting.
- The most common ADR with trastuzumab emtansine are nausea, fatigue, musculoskeletal pain, haemorrhage, headache, elevated transaminases, thrombocytopenia and peripheral neuropathy. Most of the ADR reported are severity grade 1 or 2.
- The most common ADR of grade ≥3 are thrombocytopenia, elevated transaminases, anemia, neutropenia, fatigue and hypokalaemia.

Data on comparators

The choice of comparator includes the standard in the adjuvant treatment of early breast cancer - trastuzumab.

In the budget impact analysis, trastuzumab as alternative was included as the triple combination trastuzumab + docetaxel + carboplatin, reflecting the real world clinical practice.

Pharmacoeconomic indicators

Applied analysis

The analysis aimed to evaluate the cost effectiveness of trastuzumab emtansine (Kadcyla) in the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease of the breast and/or lymph nodes after taxane-based neoadjuvant therapy and HER2-targeted therapy.

The alternative used in assessing Kadcyla (trastuzumab emtansine) is trastuzumab. The perspective and the point of view of the analysis are those of the payer - the National Health Insurance Fund (NHIF). The chosen time horizon of the model is lifelong. The method of comparative evaluation of Kadcyla (trastuzumab emtansine) health technology is a cost-utility analysis (CUA). In addition, a cost-effectiveness analysis was performed, presenting the cost per year of life gained (BGN/LYG). The health benefits for patients in the applied models were measured as life-year gained (LYG) and quality-adjusted life years (QALY). A Markov model was used to evaluate the cost effectiveness of Kadcyla (trastuzumab emtansine) in the adjuvant treatment of HER2-positive breast cancer.

Costs of the assessed health technology

The presented model includes:

- The cost of drug therapy with Kadcyla (trastuzumab emtansine)
- Cost of therapy with alternatives - trastuzumab
- Cost of medical services

The use of Kadcyla is associated with life-years (LYG) and quality-adjusted life years (QALY) gained. The results of the analysis show that the inclusion of Kadcyla (trastuzumab emtansine) in the therapeutic algorithm is a cost-effective treatment option compared to the standard - trastuzumab in patients with residual invasive disease after neoadjuvant therapy.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the payer - the National Health Insurance Fund. The time horizon of the budget impact is 5 years. Reimbursement of Kadcyla as a therapeutic alternative for adjuvant therapy of patients with residual invasive disease after neoadjuvant therapy taxane-based and HER2-targeted therapy leads to additional costs for the NHIF, without taking into account risk sharing agreements and patient access schemes.

Conclusion

Patients with HER2+ early breast cancer with residual invasive disease, after completion of preoperative systemic therapy including anti-HER2, are at increased risk of recurrence and

death as compared to those without residual invasive disease. Trastuzumab emtansine is also associated with sustained benefit in clinically relevant subgroups determined by residual tumor size, HR status, nodal status, and previous dual HER2 blockade. In addition, the safety profile of trastuzumab emtansine is consistent with the known data in MBC. The results of the budget impact analysis show an increase in the cost of adjuvant therapy of HER2+ early breast cancer.