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

HEALTH TECHNOLOGY ASSESSMENT

Mekinist 2 mg film-coated tablets x 30

INN Trametinib

Therapeutic indication(s)	Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
Start/end date of procedure	31.03.2020 - 20.11.2020
Final decision	To include a therapeutic indication in Annex 2 of the 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 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 Mekinist

Health problem

Melanoma predominantly affects young and middle-aged people, unlike most other solid tumors, mainly affecting the elderly. The average age at the time of diagnosis is 57 years, and the average age of death from the disease is 67 years. Approximately half of the cases are people between the ages of 35 and 65. In women, it is the most common cancer in the 25-29 years of age group and is second only to breast cancer in women aged 30-34. Although melanoma accounts for only 4% of all skin tumors, it causes 80% of skin cancer deaths; only 14% of patients with metastatic melanoma will live 5 years.

Even with complete surgical resection, stage III patients are at high risk for relapse and many develop metastatic disease. This necessitates adjuvant therapy to reduce the risk of progression to the metastatic stage after surgical resection. Adjuvant treatment for malignant melanoma is given after initial surgical treatment in patients with stage IIB/C and stage III.

Modern modalities for the adjuvant treatment of malignant melanoma include targeted therapy and immunotherapy.

Targeted therapies are a BRAF inhibitor (Dabrafenib) and a MEK inhibitor (Trametinib). Immunotherapies include two types of immune checkpoint inhibitors: PD-1- (Pembrolizumab and Nivolumab) and CTLA-4-inhibitors (Ipilimumab).

Immunotherapies (PD-1 inhibitors and CTLA-4 inhibitors) have not been evaluated in a clinical study for a long-term clinical benefit, particularly in BRAF (+) patients with stage III melanoma.

Current treatment guidelines in the European Union and the United States formulate recommendations for combination therapy with BRAF inhibitor and MEK inhibitor (Dabrafenib + Trametinib) as adjuvant therapy in patients with stage III malignant melanoma following complete resection, who have a BRAF V600 mutation.

Trametinib in combination with dabrafenib is indicated as adjuvant therapy in adult patients with stage III melanoma with a BRAF V600 mutation following complete resection.

Efficacy data

COMBI-AD clinical trial is a randomized, placebo-controlled, double-blind, phase III clinical trial of dabrafenib + trametinib in the adjuvant treatment of patients with stage III melanoma with BRAF V600E or V600K mutations after complete resection. The main goal of the study

was to evaluate the efficacy of the combination therapy over placebo on the primary endpoint relapse-free survival (RFS).

RFS values were higher in the dabrafenib + trametinib group compared to the placebo group during the 5-year follow-up period: in the first year: 88% of patients had no relapse versus 56% of placebo; at year 5: 52% of patients in the dabrafenib + trametinib group had no relapse. This means that more than half of the patients are alive and without a recurrence of the disease at year 5. Adjuvant therapy with dabrafenib and trametinib for 1 year resulted in a 49% lower risk of relapse or death.

A *Cure-rate model for RFS* was also used for COMBI-AD to assess the long-term benefit of adjuvant treatment with dabrafenib and trametinib. In the COMBI-AD study, the cure-rate model demonstrated the long-term benefit of one-year adjuvant treatment with Dabrafenib and Trametinib.

At 36 months, the difference in RFS between dabrafenib and trametinib was 20% compared with placebo, accompanied by a reduced incidence of adverse events. At the 48th month the difference is 17%, and at the 60th month it is 16%.

At year 5, 65% of patients are alive and without distant metastases. Adjuvant therapy with dabrafenib and trametinib reduces the risk of distant metastases or death by 45% compared with placebo. In terms of overall survival, 86% of patients are alive at month 36.

The Health-related Quality of Life (HRQoL) analysis using EQ-5D in the COMBI-AD clinical study did not show a statistically significant difference between dabrafenib + trametinib groups and placebo.

An indirect comparison of dabrafenib + trametinib targeted combination therapy vs pembrolizumab and nivolumab showed the lowest percentage of adjuvant patients who relapsed during treatment in the first year - with dabrafenib + trametinib only 5% of patients, in pembrolizumab adjuvant therapy - 21% of patients relapsed in the first year; in nivolumab adjuvant therapy the percentage is 27%.

Safety data

The most common types of ADRs reported in dabrafenib + trametinib group were general disorders and administration site conditions (85%), skin and subcutaneous tissue disorders (75%) and gastrointestinal disorders (74%), all of these are more common than those in the placebo group. Of the ADRs reported in > 10% of participants receiving dabrafenib + trametinib, pyrexia was the most frequent, observed at any grade in 63% of participants and at grade 3 or 4 in 5% of participants. Fatigue, nausea, headache, chills and diarrhea (any grade)

occurred in more than 30% of dabrafenib + trametinib participants, but ≤4% of these events were grade 3 or 4.

Data on comparators

A comparator is the medicinal product Keytruda (Pembrolizumab), as at the time of evaluation it was the only medicinal product included in the PDL for the adjuvant treatment of adults with stage III melanoma and lymph node involvement following complete resection.

Pharmacoeconomic indicators

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

The governmental institutions of Sweden, France, Germany and the United Kingdom issued a positive assessment and included Mekinist in the list of medicinal products subject to reimbursement. NICE and AWMSG (Wales) recommend the health technology for routine treatment.

Applied analysis

The selected methods for comparative assessment of the health technology are cost-utility economic analysis (CUA) and cost-effectiveness analysis (CEA). A long-term outcome measure life expectancy was used, health-related improvement was reported as quality adjusted life year. The perspective of the analysis is that of the payer - the National Health Insurance Fund (NHIF). The chosen time horizon is 50 years. Health benefits and costs are discounted at an annual discount rate of 3.5%. A non-homogeneous, semi-Markov cohort model was employed with defined health conditions: recurrence, previous treatments and death. According to the national therapeutic practice, the medicinal product Keytruda (Pembrolizumab) is currently the only medicinal product included in the PDL for adjuvant treatment of adults with stage III melanoma and lymph node involvement following a complete resection. The results of the cost-utility and cost-effectiveness analyses show that the combination of dabrafenib + trametinib showed lower values for QALY and LYG compared to pembrolizumab, but also a lower cost. In terms of mechanism of action, dabrafenib + trametinib therapy is considered to be alternative-free, as it is a targeted therapy represented by a BRAF inhibitor (dabrafenib) and an MEK inhibitor (trametinib).

Cost of the assessed health technology

The direct medical cost of drug therapy with the alternatives is included.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying institution, the NHIF. The time horizon is 5 years. The expected number of patients for the

first year is 5, and for the fifth it reaches 9. The reimbursement of the health technology will increase the budget over a five-year period, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The assessment of the pharmacoeconomic parameters of dabrafenib + trametinib combination for adjuvant therapy in adult patients with stage III melanoma with BRAF V600 mutation, following a complete resection, shows that the combination has lower QALY and LYG values, compared to pembrolizumab, but also lower cost.

The budget impact analysis shows that on reimbursement of the combination dabrafenib + trametinib for the specified indication, an additional cost is expected for the payer.